PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 471/04, A61K 31/435 // (C07D 471/04, 221:00, 209:00)

A1

(11) International Publication Number: WO 99/21859

(43) International Publication Date: 6 May 1999 (06.05.99)

(21) International Application Number: PCT/EP98/06357

(22) International Filing Date: 8 October 1998 (08.10.98)

(30) Priority Data:
9721437.3 10 October 1997 (10.10.97) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CHEUNG, Mui [CN/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). GLENNON, Kimberly, Caroline [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). LACKEY, Karen, Elizabeth [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). PEEL, Michael, Robert [GB/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).

(74) Agent: REED, Michael, A.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

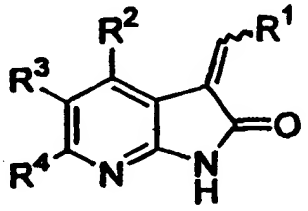
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AZAOXINDOLE DERIVATIVES

(57) Abstract

Compounds of formula (I) where R_1 is optionally substituted phenyl or an optionally substituted phenyl or an optionally substituted heterocyclic ring selected from pyrrole, furan, thiophene, pyrazole or indole are useful as protein kinase inhibitors in diseases characterized by cellular proliferation.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

AZAOXINDOLE DERIVATIVES

FIELD OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds generally pharmacologically useful as agents which inhibit protein kinases, and which compounds can be characterized as substituted pyrrolopyridinones. The pharmacological activities of the claimed compounds are useful in the treatment of mammals, for example in the treatment of psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and cancer.

More specifically, the present invention is directed to methods of regulating, modulating, or inhibiting protein kinases of both the receptor and non-receptor types, for the prevention and/or treatment of disorders related to unregulated protein kinase activity, including cell proliferative disorders, metabolic disorders and excessive cytokine production disorders. The compounds of the present invention can also be used in the treatment of certain forms of cancer, can be used to provide additive or synergistic effects with certain existing cancer chemotherapies, and/or be used to restore effectiveness of certain existing cancer chemotherapies and radiation. At the present time, there is a need in the areas of diseases characterized by cell proliferation for such therapeutic agents.

BACKGROUND OF THE INVENTION

Protein kinases play a critical role in the control of cell growth and differentiation (Schlessinger and Ullrich, 1992, Neuron, 9:383-391). A partial non-limiting list of such kinases includes ab1, ATK, bcr-ab1, Blk, Brk, Btk, c-fms, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie_1, tie_2, TRK, UL97, VEGFR, Yes and Zap70. Aberrant expression or mutations in

protein kinases have been shown to lead to either uncontrolled cell proliferation (for example, malignant tumour growth) or to defects in key developmental processes. Protein kinases are critical to the control, regulation, and modulation of cell proliferation in the diseases and disorders associated with abnormal cell proliferation, therefore the inhibition of protein kinases is an object of the present invention.

Additionally, protein kinases have been implicated as targets in central nervous system disorders (such as Alzheimer's), inflammatory disorders (such as psoriasis), bone diseases (such as osteoporosis), atheroscleroses, restenosis, thrombosis, metabolic disorders (such as diabetes) and infectious diseases (such as viral and fungal infections).

One of the most commonly studied pathways involving kinase regulation is cellular signalling from receptors at the cell surface to the nucleus (Crews and Erikson, 1993). The function of each receptor kinase is determined by its pattern of expression, ligand availability, and the array of downstream signal transduction pathways that are activated by a particular receptor. One example of this pathway includes a cascade of kinases in which members of the Growth Factor receptor Tyrosine Kinases (such as EGF-R, PDGF-R, VEGF-R, IGF1-R, the Insulin receptor), deliver signals through phosphorylation to other kinases such as Src Tyrosine kinase, and the Raf, Mek and Erk serine/threonine kinase families (Crews and Erikson, 1993; Ihle et al., 1994). Each of these kinases is represented by several family members (Pelech and Sanghera, 1992) which play related, but functionally distinct roles. The loss of regulation of the growth factor signalling pathway is a frequent occurrence in cancer (Fearon, *Genetic lesions in human cancer*, in Molecular Oncology; 1996, 143-178) as well as other disease states.

Ras genes are mutated with the following frequencies such as those in this partial non-limiting list of primary human tumors: lung (adenocarcinoma), 30%; colon (adenocarcinoma), 50%; pancreatic carcinoma, 90%; seminoma, 40%; thyroid, 50% (McCormick, *Ras oncogenes* in Oncogenes and the molecular origins of cancer: 1989, 125-146) . The raf1 serine/threonine kinase can be activated by the known oncogene product *ras*. The raf kinase enzyme

positively regulates cell division through the Raf/MEK/ERK protein kinase cascade. This activation is the result of cRaf1 catalyzed phosphorylation of the protein kinase, MEK1. MEK1 phosphorylates and activates the protein kinase ERK (alternatively known as p42/MAP kinase protein). ERK phosphorylates and regulates transcription factors required for cell division (Avruch et al, TIBS; 1994 (19) 279-283). cRaf1 negatively regulates cell death by modulation of the activity of Bcl-2, a critical regulator of apoptosis. This regulation involves direct phosphorylation of Bcl-2 family members (Gajewski and Thompson, Cell: 1996 (87) 619-628). Both of these aspects of cRaf1 mediated regulation of cellular proliferation require the kinase activity of cRaf1. In addition, Raf anti-sense literature teaches that the reduction of Raf protein levels correlates with a reduction in tumor growth rate in *vivo* tumor mouse models (Monia, Johnston, Geiger, Muller, and Fabro, Nature Medicine, volume 2, number 6, June 1996, 668-674). Inhibitors of the kinase activity of cRaf1 should therefore provide effective treatment for a wide variety of common human cancers.

Activation of the MAP kinase signalling pathway represents an attractive target for tumor therapy by inhibiting one, or several, of the kinases involved. An additional member of the MAP kinase family of proteins is the p38 kinase (alternatively known as cytokine suppressive drug binding protein [CSBP™] or reactivation kinase[RK]). Activation of this kinase has been implicated in the production of proinflammatory cytokines such as IL-1 and TNF. Consequently, inhibition of this kinase could offer a treatment for disease states in which disregulated cytokine production is involved.

The signals mediated by kinases have also been shown to control cell growth, cell death and differentiation in the cell by regulating the processes of the cell cycle (Massague and Roberts, 1995). Progression through the eukaryotic cell cycle is controlled by a family of kinases called cyclin dependent kinases (CDKs) (Myerson et al., 1992). The regulation of CDK activation is complex, but requires the association of the CDK with a member of the cyclin family of regulatory subunits (Draetta, 1993; Murray and Kirschner, 1989; Solomon et al., 1992). A further level of regulation occurs through both activating and inactivating phosphorylations of the CDK subunit (Draetta, 1993; Ducommun

et al., 1991; Gautier et al., 1989; Gould and Nurse, 1989; Krek and Nigg, 1991; Murray and Kirschner, 1989; Solomon et al., 1992; Solomon et al., 1990). The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle (Pines, 1993; Sherr, 1993). Both the critical G1-S and G2-M transitions are controlled by the activation of different cyclin/CDK activities. In G1, both cyclin D/CDK4 and cyclin E/CDK2 are thought to mediate the onset of S-phase (Matsushime et al., 1994; Ohtsubo and Roberts, 1993; Quelle et al., 1993; Resnitzky et al., 1994). Progression through S-phase requires the activity of cyclin A/CDK2 (Girard et al., 1991; Pagano et al., 1992; Rosenblatt et al., 1992; Walker and Maller, 1991; Zindy et al., 1992) whereas the activation of cyclin A/*cdc2* (CDK1) and cyclin B/*cdc2* are required for the onset of metaphase (Draetta, 1993; Girard et al., 1991; Murray and Kirschner, 1989; Pagano et al., 1992; Rosenblatt et al., 1992; Solomon et al., 1992; Walker and Maller, 1991; Zindy et al., 1992). It is not surprising, therefore, that the loss of control of CDK regulation is a frequent event in hyperproliferative diseases and cancer. (Hunter and Pines, 1994; Lees, 1995; Pines, 1992)

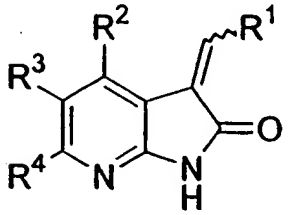
Inhibitors of kinases involved in mediating or maintaining particular disease states represent novel therapies for these disorders. Examples of such kinases include, but are not limited to: (1) inhibition of Src (Brickell, 1992; Courtneidge, 1994), raf (Powis, 1994) and the cyclin-dependent kinases (CDKs) 1, 2 and 4 in cancer (Hunter and Pines, 1994; Lees, 1995; Pines, 1992), (2) inhibition of CDK2 or PDGF-R kinase in restenosis (Buchdunger et al., 1995), (3) inhibition of CDK5 and GSK3 kinases in Alzheimers (Aplin et al., 1996; Hosoi et al., 1995), (4) inhibition of c-Src kinase in osteoporosis (Tanaka et al., 1996), (5) inhibition of GSK-3 kinase in type-2 diabetes (Borthwick et al., 1995); (6) inhibition of the p38 kinase in inflammation (Badger et al., 1996); (7) inhibition of VEGF-R 1-3 and TIE-1 and -2 kinases in angiogenesis (Shawver et al., 1997); (8) inhibition of UL97 kinase in viral infections (He et al., 1997); (9) inhibition of CSF-1R kinase in bone and hematopoetic diseases (Myers et al., 1997), and (10) inhibition of Lck kinase in autoimmune diseases and transplant rejection (Myers et al., 1997).

It is an object of the present invention to provide potent, specific, orally, intravenously, or subcutaneously active small molecule inhibitors of the signal transduction activity of protein kinases for the treatment of human malignancies, for example, one or more of breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, genitourinary tract (including bladder and prostate), ovarian, gastric, bone, or pancreatic tumors, using the compounds of the present invention, methods of their administration, methods of their formulation, and methods of their synthesis.

The compounds of the present invention are additionally useful in the treatment of one or more diseases afflicting mammals which are characterized by cellular proliferation in the areas of blood vessel proliferative disorders, fibrotic disorders, mesangial cell proliferative disorders and metabolic diseases. Blood vessel proliferative disorders include arthritis and restenosis. Fibrotic disorders include hepatic cirrhosis and atherosclerosis. Mesangial cell proliferative disorders include glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection and glomerulopathies. Metabolic disorders include psoriasis, diabetes mellitus, chronic wound healing, inflammation and neurodegenerative diseases.

SUMMARY OF THE INVENTION

In summary, the invention includes a family of compounds having the general structural formula (I):



(I)

wherein:

R^1 is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R^5, C (O)R^5, C(O)OR^5, and OR^5, where Het and R^5 are as defined below;

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -N$R^5CO_2R^5$, -NR^5CONR^5R^7, -N$R^5SO_2R^5$, -NR^5C (NR^5)NHR^5, -COR^5, -CO_2R^5, -CONR^5R^7, -SO_2NR^5R^7, -OCONR^5R^7, or -C(NR^5)NR^5R^7, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -$S(O_2)$-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -N$R^5CO_2R^5$, -NR^5CONR^5R^7, -N$R^5SO_2R^5$, -NR^5C(NR^5)NHR^5, -COR^5, -CO_2R^5, -CONR^5R^7, -SO_2NR^5R^7, aryl-SO_2NR^5R^7, -OCONR^5R^7, or -C(NR^5)NR^5R^7, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -$S(O_2)$-, and -N(R^5)-, where said Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -N$R^5CO_2R^5$, -NR^5CONR^5R^7, -N$R^5SO_2R^5$, -NR^5C(NR^5)NHR^5, -COR^5, -CO_2R^5, -CONR^5R^7, -SO_2NR^5R^7, -OCONR^5R^7, or -C(NR^5)NR^5R^7, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -$S(O_2)$-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-12} aliphatic, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -$S(O_2)$-, and -N(R^6)-, where said C_{1-12} aliphatic,

aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$, where substituted Het and substituted aryl bear substituents that are any of -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-12} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

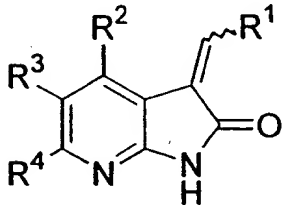
Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to

one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A preferred group of compounds of the present invention are those of the structural formula



(I)

wherein:

R^1 is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R^5, $C(O)R^5$, $C(O)OR^5$, and OR^5, where Het and R^5 are as defined below;

R^2 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, $-S(O)-$, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-6} aliphatic, CN, NO_2, halogen, $-OR^5$, $-SR^5$,

$-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl-$SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of

$-C(O)-$, $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, and $-N(R^5)-$, where said Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of $-C(O)-$, $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-6} aliphatic, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, and $-N(R^6)-$, where said C_{1-6} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$, where substituted Het and substituted aryl bear substituents that are any of -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-6} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

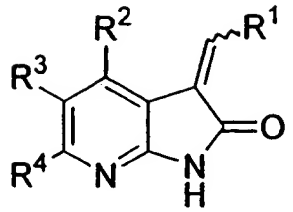
R^7 is H or R^5;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A highly preferred group of compounds of the present invention are those of the general formula (I)



(I)

wherein:

R^1 is Het or aryl, with said Het or aryl optionally substituted by one to four substituents selected from the group consisting of C_{1-6} lower alkyl, halogen, $-(CH_2)_{1-6}$ OH, $-O(CH_2)_3N(CH_3)_2$, $-NO_2$, $-OR^5$, $-NH(CO)CH_3$, $-C(O)R^5$, aryloxy, $-C_6H_5SO_2NH_2$, or $-C(O)OR^5$, where Het and R^5 are as defined below;

R^2 is H;

R^3 is Het, Het-R^5, aryl, C_{1-12} aliphatic, $-COR^5$, $-CO_2R^5$, or halogen, and where Het and R^5 are as defined below;

R^4 is H;

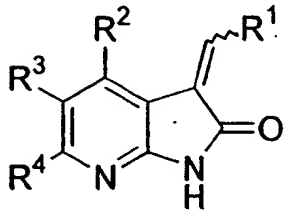
R^5 is H, C_{1-12} aliphatic, $-SO_2R^6$, or $-N(R^6)_2$, where said C_{1-12} aliphatic is optionally substituted by one to four of halogen, where R^6 is as defined below;

R^6 is H, or NH_2;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A group of compounds that are preferred with respect to their substituents at R^1 are compounds of the formula:



(I)

wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, $-O-C_6H_5$, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$;

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO_2, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl-$SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, where said Het, aryl

or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-12} aliphatic, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^6)-$, where said C_{1-12} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$, where substituted Het and substituted aryl are any of -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-12} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

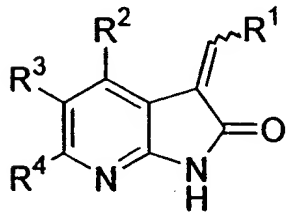
Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole,

isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

Another group of compounds that are preferred with respect to their substituents at Position R^1 are compounds of the structural formula



(I)

wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, -O-C_6H_5, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or -C_6H_5-SO_2NH_2 ;

R^2 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-6} aliphatic, CN, NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, aryl-$SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, where said Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-6} aliphatic, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^6)-, where said C_{1-6} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO_2, -R^6, -SR^6, -OR^6, -N(R^6)$_2$, -S(O)R^6, -SO_2R^6, -SO_2N(R^6)$_2$, NR^6COR^6, -NR^6CON(R^6)$_2$, -NR^6(NR^6)NHR^6, -CO_2R^6, -CON(R^6)$_2$, -N$R^6$$SO_2R^6$, -OCON($R^6$)$_2$, or -N$R^6$$CO_2R^6$, where substituted Het and substituted aryl are any of -CN, -NO_2, -R^6, -SR^6, -OR^6, -N(R^6)$_2$, -S(O)R^6, -SO_2R^6, -SO_2N(R^6)$_2$, NR^6COR^6, -NR^6CON(R^6)$_2$, -NR^6(NR^6)NHR^6, -CO_2R^6, -CON(R^6)$_2$, -N$R^6$$SO_2R^6$, -OCON($R^6$)$_2$, or -N$R^6$$CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-6} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

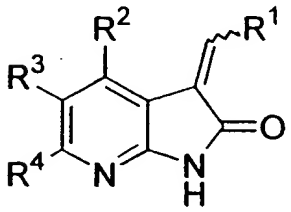
Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated

heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

Yet another group of compounds that are preferred with respect to their substituents at position R^1 are compounds of the structural formula



(I)

wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, -O-C_6H_5, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or -C_6H_5-SO_2NH_2;

R^2 is H;

R^3 is Het, Het-R^5, aryl, C_{1-12} aliphatic, -COR^5, -CO_2R^5, or halogen, and where Het and R^5 are as defined below;

R^4 is H;

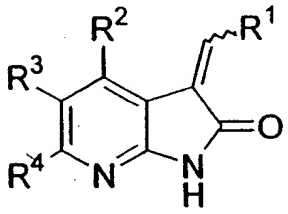
R^5 is H, C_{1-12} aliphatic, $-SO_2R^6$, or $-N(R^6)_2$, where said C_{1-12} aliphatic is optionally substituted by one to four of halogen, where R^6 is as defined below;

R^6 is H, or NH_2;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

Still another group of compounds that are preferred with respect to their substituents at position R^1 are compounds of the structural formula



(I)

wherein:

R^1 is phenyl, substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of Br, F, -OH, $-CH_2OH$, $-O-CH_3$, $-O-C_6H_5$, $-O-(CH_2)_3NH_2$, $-C(CH_3)_2$, or $-NHCOCH_3$, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$.

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$,

$-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO_2, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl-$SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, where said Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-12} aliphatic, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^6)-$, where said C_{1-12} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$, where substituted Het and substituted aryl are any of -CN, $-NO_2$, $-R^6$, $-SR^6$, $-OR^6$, $-N(R^6)_2$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^6)_2$, NR^6COR^6, $-NR^6CON(R^6)_2$, $-NR^6(NR^6)NHR^6$, $-CO_2R^6$, $-CON(R^6)_2$,

$-NR^6SO_2R^6$, $-OCON(R^6)_2$, or $-NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-12} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

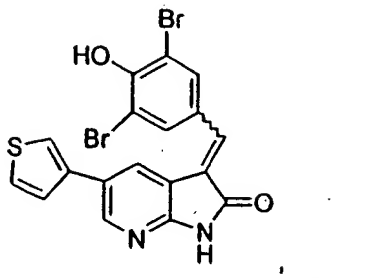
R^7 is H or R^5;

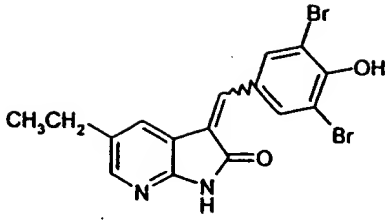
Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyrrole, furan, thiophene, pyrazole, or indole;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

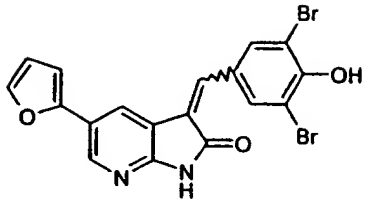
and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A preferred sub-group of compounds includes those of the following structural formula:

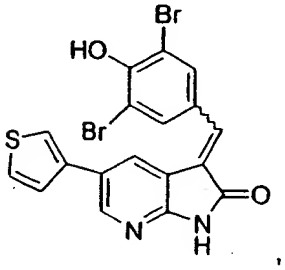


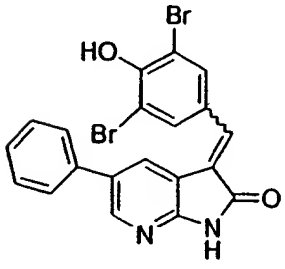


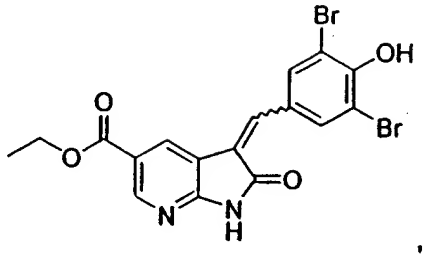
and

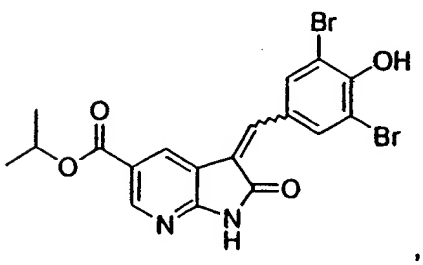


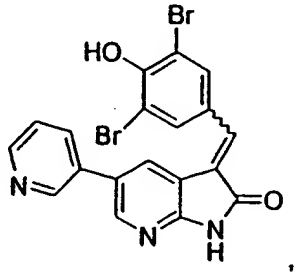
Another preferred sub-group of compounds includes those of the following structural formula:

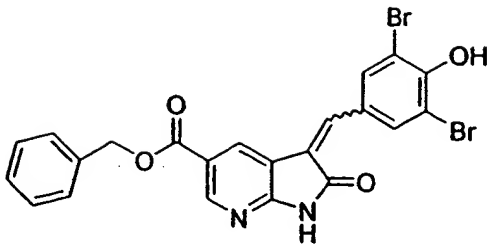
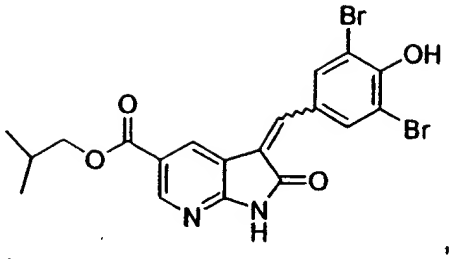
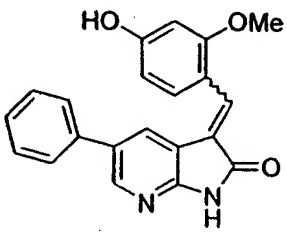
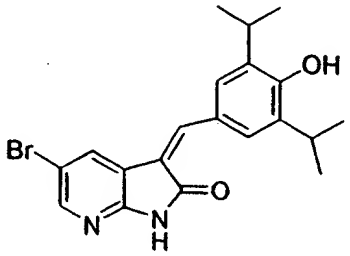
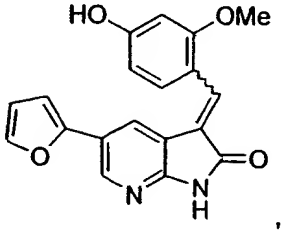
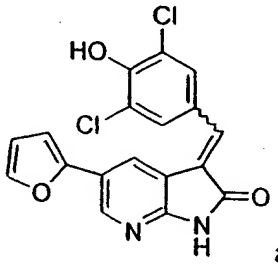
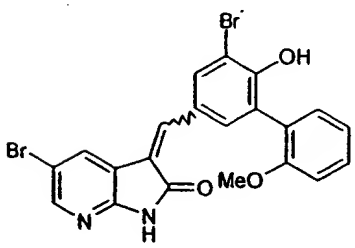










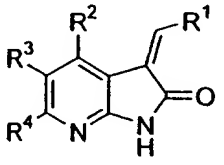






and


Certain compounds of formula (I) above may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

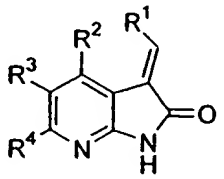
Due to the presence of a double bond, also included in the compounds of the invention are their respective pure E and Z geometric isomers as well as mixtures of E and Z isomers.

The invention as described and as claimed does not set any limiting ratios on prevalence of Z to E isomers.

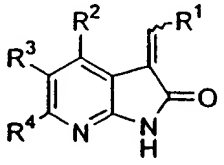
Thus, compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, (compound number 7 in the tables below), is disclosed and claimed as the E geometric isomer thereof, the Z geometric isomer and a mixture of the E and Z geometric isomers thereof, but not limited by any given ratio(s).



Z-isomer



E-isomer



E/Z mixture

Certain of the compounds as described will contain one or more chiral atoms or chiral groups and therefore be either dextrorotary or levorotary. Also included in the compounds of the invention are the respective dextrorotary or levorotary pure preparations, and racemic mixtures thereof.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in the compound of formula (I). The therapeutic activity of the invention resides in the moiety derived from the compound of the invention as defined herein and the identity of another component, such as a salt cation, is of less importance although for

therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient.

Highly preferred biohydrolyzable carbamates comprise compounds of formula (I), wherein R^1 is phenyl substituted at the para- position by OH and said OH is conjugated with a carbamoyl conjugate to yield a biohydrolyzable carbamate wherein said carbamoyl conjugate is selected from the group consisting of diethylaminocarbonyl, N-(2-hydroxyethyl)aminocarbonyl, N,N,-bis(2-hydroxyethyl)aminocarbonyl, hydroxyethyloxyethylaminocarbonyl, 4-morpholinocarbonyl and 4-methyl-1-piperazinylcarbonyl.

Highly preferred biohydrolyzable carbonates comprise compounds of formula (I), wherein R^1 is phenyl substituted at the para- position by OH and said OH is conjugated with a carbonate conjugate to yield a biohydrolyzable carbonate wherein said carbonyl conjugate is selected from the group consisting of phenylmethyloyxcarbonyl, ethyloxycarbonyl, isobutyloxycarbonyl, and pyridinemethyloxycarbonyl.

Highly preferred biohydrolyzable esters comprise compounds of formula (I), wherein R^1 is phenyl substituted at the para- position by OH and said OH is conjugated with an ester conjugate to yield a biohydrolyzable ester wherein said ester conjugate is selected from the group consisting of t-butylcarbonyloxymethyl.

Independent Substituents

The invention discloses four different points of substitution on structural formula (I). Each of these points of substitution bears a substituent whose selection and synthesis as part of this invention was independent of all other points of substitution on formula (I). Thus, each point of substitution is now further described individually.

R^1 is a selected heterocyclic ring, an aryl ring, or a biaryl ring. Any of these ring types can be optionally substituted by up to four substituents. These

substituents can be selected from among R^5, which is defined further below; carbonyl-R^5; ester-R^5; and ether-R^5.

R^1 is alternatively a selected heterocyclic ring, or an aryl ring, which can be substituted by up to four substituents selected from a group consisting of 1 to 6 carbon lower alkyl, halogen, 1-6 carbon lower alkyl substituted hydroxyl, nitro, ether-R^5, carboxyl-R^5, aryloxy, sulfonamide substituted phenyl, ether-alkyl substituted by amine, amide substituted by alkyl, or ester-R^5. Suitable heterocyclic rings include pyridine, pyrrole, furan, quinoline, thiophene and thiazole.

R^1 is preferably substituted phenyl, a heterocyclic ring, or a substituted heterocyclic ring. Suitable phenyl substituents include halogen, 1-6 carbon lower alkyl, hydroxy, 1-6 carbon lower alkyl hydroxy, 1-6 carbon lower alkoxy, phenoxy, 1-6 carbon lower alkoxy substituted by amine, or amide substituted by 1-6 carbon lower alkyl. Suitable heterocyclic ring substituents include methyl and sulfonamide phenyl.

Most preferably, R^1 is substituted phenyl or a substituted heterocyclic ring. Suitable phenyl substituents include one or more of bromine, fluorine, hydroxyl, hydroxymethyl, methoxy, phenoxy, aminopropyloxy, isopropyl or methylamido. Suitable heterocyclic substituents include one or more of methyl or sulfonamide phenyl.

R^2 is a heterocyclic ring, a fused heterocyclic ring system, aryl, a 1-12 carbon aliphatic chain, cyanbo, nitro, halogen, ether-R^5, thioether-R^5, sulfenyl-R^5, amine-R^5R^7, amide-$(R^5)_{1-3}$, carbamate-$(R^5)_{1-2}$, ureate-$(R^5)_{1-2}$, sulfonamide-$(R^5)_{1-2}$, carbonyl-R^5, ester-$(R^5)_{1-2}$, amide-R^5R^7, or sulfonamide-R^5R^7. The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfine, sulfone, carbonyl, or R^5-substituted nitrogen. These aryl, heterocyclic and fused heterocyclic rings and these aliphatic chains can be substituted by 1 to 3 occurences of R^5.

More preferably, R^2 comprises aliphatic chains of 1 to 6 carbons.

Most preferably, R^2 is hydrogen.

R^3 is a heterocyclic ring, a fused heterocyclic ring system, aryl, a 1-12 carbon aliphatic chain, cyanbo, nitro, halogen, ether-R^5, thioether-R^5, sulfenyl-R^5, amine-R^5R^7, amide-$(R^5)_{1-3}$, carbamate-$(R^5)_{1-2}$, ureate-$(R^5)_{1-2}$, sulfonamide-$(R^5)_{1-2}$, carbonyl-R^5, ester-$(R^5)_{1-3}$, amide-R^5R^7, or sulfonamide-R^5R^7. The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfine, sulfone, carbonyl, or R^5-substituted nitrogen. These aryl, heterocyclic and fused heterocyclic rings and these aliphatic chains can be substituted by 1 to 3 occurences of R^5.

R^3 is more preferably an aryl ring, a heterocyclic ring, a substituted heterocyclic ring, a 1 to 12 carbon aliphatic chain, carbonyl-R^5, ester-R^5, or halogen.

R^4 is a heterocyclic ring, a fused heterocyclic ring system, aryl, a 1-12 carbon aliphatic chain, cyanbo, nitro, halogen, ether-R^5, thioether-R^5, sulfenyl-R^5, amine-R^5R^7, amide-$(R^5)_{1-3}$, carbamate-$(R^5)_{1-2}$, ureate-R^5, sulfonamide-$(R^5)_{1-2}$, carbonyl-R^5, ester-R^5, amide-R^5R^7, or sulfonamide-R^5R^7. The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfine, sulfone, carbonyl, or R^5-substituted nitrogen. These aryl, heterocyclic and fused heterocyclic rings and these aliphatic chains can be substituted by 1 to 3 occurences of R^5.

Most preferably, R^4 is hydrogen.

R^5 is hydrogen, a heterocyclic ring, an aryl ring, halogen, amino-R^6 or a 1-12 carbon aliphatic chain. The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfine, sulfone, carbonyl, or R^5-substituted nitrogen. The heterocylic ring, aryl ring or aliphatic chain can be substituted by from one to four of halogen, another heterocyclic ring or substituted heterocyclic ring, an aryl ring, a substituted aryl ring, cyano, nitro, R^6, ether-R^6, thioether-R^6, amine-$(R^6)_{1-3}$, sulfenyl-R^6, sulfonyl-R^6, sulfonamide-$(R^6)_{1-2}$, ester-R^6, amide-$(R^6)_{1-3}$, carbonate-$(R^6)_{1-2}$, carbamate-$(R^6)_{1-2}$. The aforesaid substituted heterocyclic or substituted aryl rings can likewise be substituted by

any of cyano, nitro, R^6, ether-R^6, thioether-R^6, amine-$(R^6)_{1-3}$, sulfenyl-R^6, sulfonyl-R^6, sulfonamide-$(R^6)_{1-2}$, ester-R^6, amide-$(R^6)_{1-3}$, carbonate-$(R^6)_{1-2}$, carbamate-$(R^6)_{1-2}$.

R^5 is more preferably hydrogen, 1-12 carbon aliphatic, sulfonyl-R^6, or amine-$(R^6)_2$. The aliphatic chain can be substituted by one to four occurences of a halogen.

R^6 hydrogen, 1-12 carbon aliphatic, an aryl ring or a heterocylic ring. The aryl or heterocyclic rings can be substituted by 1 to 3 occurences of a halogen or a hydroxyl.

Preferably, R^6 is hydrogen or amine.

R^7 is hydrogen or R^5.

Heterocyclic rings are suitably selected from the group of the following rings useful in medicinal chemistry: acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane.

Heterocyclic rings are more preferably selected from the group consisting of pyrrole, furan, thiophene, pyrazole, indole, pyridine or quinoline.

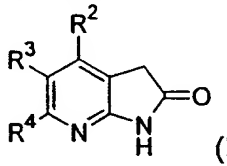
Fused heterocyclic ring systems include the structure where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the

group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5.

In a further aspect, the invention provides a process for the preparation of a compound of the formula (I), which process comprises the reaction of a compound of the formula (II)

R^1CHO (II)

with a compound of the formula (III)



(III), wherein all substituents are as defined above.

The reaction is conveniently carried out in the presence of a catalytic acid in the presence of a suitable inert solvent, for example an aromatic hydrocarbon or a halogenated hydrocarbon at a non-extreme temperature, for example from 0 °C to 150 °C, preferably 80 °C to 110 °C. Optionally the reaction is carried out in the presence of a strong acid, for example hydrochloric acid or sulfuric acid, in acetic acid as the solvent. Alternatively, the reaction may be carried out in the presence of a base, for example the treatment of (II) and (III) with a catalytic amount of piperidine in ethyl alcohol at temperatures between 22 °C and 78 °C.

The preparation of compounds (II) and (III) is known to those skilled in the art and many compounds having formula (II) are commercially available. (Jutz, Adv. Org. Chem., 9, 225-342, 1975; Truce, Org. React., 9, 37-72. 1957, Marfat, A.; Carta, M. P. Tetrahedron Letters 1987, 28, 4027 and references cited therein).

In addition to the above, one compound within the genus of formula (I) may be converted to another compound within the genus of formula (I) by chemical transformation of the appropriate substituent or substituents.

The compounds and salts of formula (I) have pharmacological activity as demonstrated hereinafter by their inhibition of protein kinase enzyme(s). It has thus been established that compounds of the present invention are of potential use in medicine. The present invention thus also provides compounds of formula (I) and pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates thereof (hereinafter identified as the 'active compounds') for use in medical therapy, and particularly in the treatment of disorders mediated by protein kinase activity such as human malignancies. The compounds are especially useful for the treatment of disorders which are caused by mutated ras and upregulated tyrosine kinase signalling pathways such as breast, ovarian, colon, lung (including non-small cell lung), pancreatic, prostate, and gastric cancers.

According to a further aspect of the present invention there is provided a method of treating a disease mediated by a mitogen activated protein kinase, comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

According to a further aspect of the present invention there is provided a method of treating a disease mediated by a kinase selected from the group consisting of ab1, ATK , bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6 , cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie_1, tie_2, TRK, UL97, Yes and Zap70, comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound of formula (I) or a

pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

According to a further aspect of the present invention there is provided a method of treating a disease meditated by a kinase selected from the group consisting of cRaf1 kinase, p38 kinase, VEGFR kinase, Tie2 kinase and c-fms kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

According to a further aspect of the present invention there is provided a method of inhibiting tumor growth, preventing organ transplant rejection, healing a chronic wound, or of treating a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation, and neurodegenerative disease, comprising the step of administering to a patient in need thereof a pharmacologically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

According to a further aspect of the present invention there is provided a method for the treatment of susceptible malignancies in an animal, e.g. a human, which comprises administering to the animal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by protein kinase activity.

The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by disorders caused by a mutated ras gene.

The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by an upregulated tyrosine kinase signalling pathway.

The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by a mitogen activated protein kinase.

The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by cRaf kinase.

The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for inhibiting tumor growth, preventing organ transplant rejection, healing a chronic wound, or of treating

a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation, and neurodegenerative disease.

Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of malignant tumors.

Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of blood vessel proliferative disorders such as angiogenic and vasculogenic disorders in cancer, ocular diseases, and restenosis.

Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of fibrotic disorders such as mesangial cell proliferative disorders.

Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of viral or eukaryotic infections.

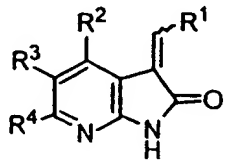
Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of inflammatory disorders.

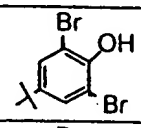
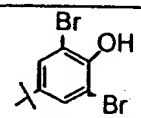
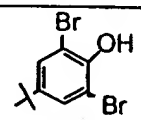
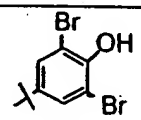
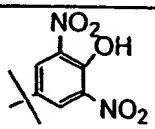
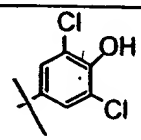
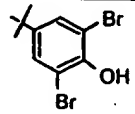
Another aspect of the present invention provides the use of an active compound of formula (I) in coadministration with previously known anti-tumor therapies for more effective treatment of such tumors.

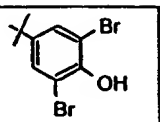
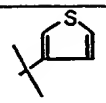
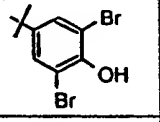
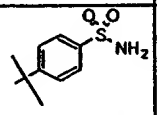
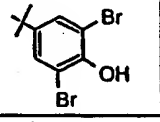
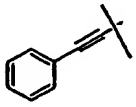
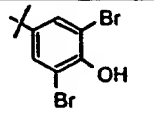
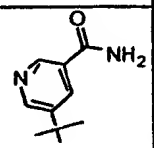
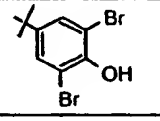
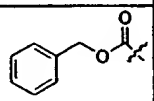
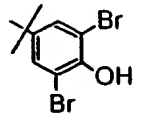
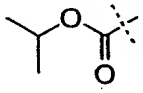
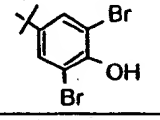
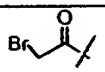
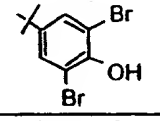
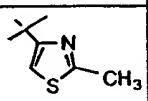
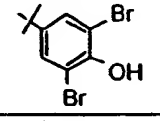
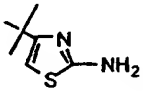
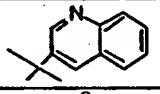
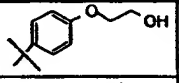
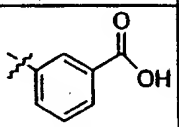
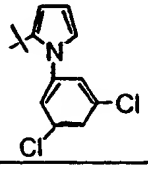
Compounds we have synthesized as part of the present invention which are currently preferred are listed in Tables 1, 1A, 2 and 2A, set forth below. Compounds are identified by the numbers shown in the first column; variables below in the rest of the columns are with reference to the generic structure (I).

Corresponding IUPAC nomenclature are disclosed in Tables 2 and 2A, respectively, below. Since all substituents at each point of substitution are capable of independent synthesis of each other, the tables are to be read as a matrix in which any combination of substituents is within the scope of the disclosure and claims of the invention.

Table 1



Number	R^1	R^2	R^3	R^4
1		H		H
2		H		H
3		H		H
4		H		H
5		H	Br	H
6		H	Br	H
7		H		H

8		H		H
9		H		H
10		H		H
11		H		H
12		H		H
13		H		H
14		H		H
15		H		H
16		H		H
17		H	Br	H
18		H	Br	H
19		H	Br	H
20		H	Br	H

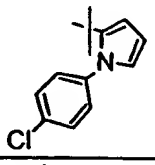
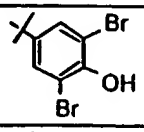
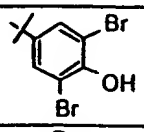
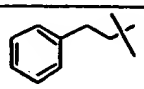
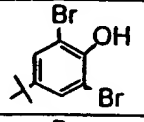
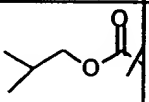
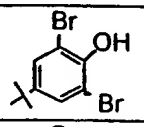
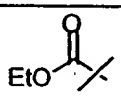
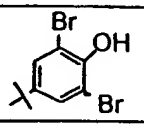
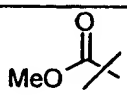
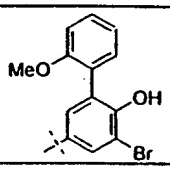
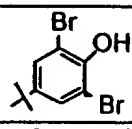
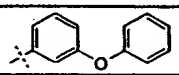
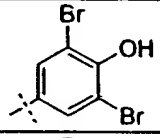
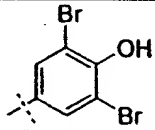
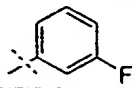
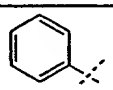
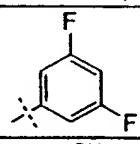
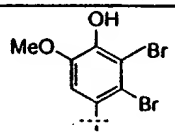
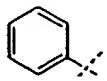
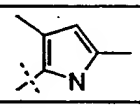
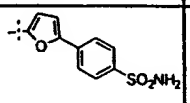
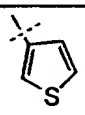
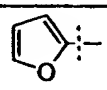
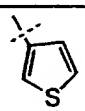
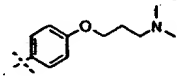
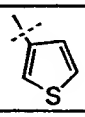
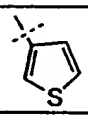
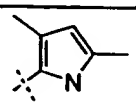
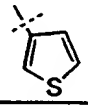
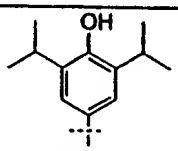
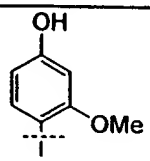
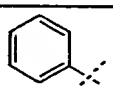
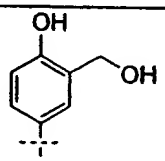
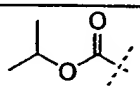
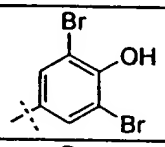
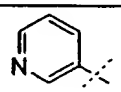
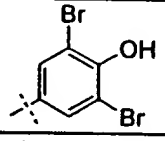
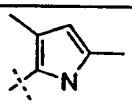
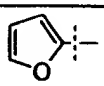
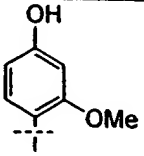
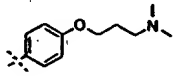
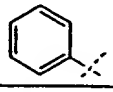
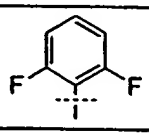
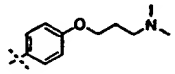
21		H	Br	H
22		H	$-CH_2CH_3$	H
23		H		H
24		H		H
25		H		H
26		H		H
27		H	Br	H

Table 1A

Number	R^1	R^2	R^3	R^4
28		H	Br	H
29		H	Br	H
30		H	H	Cl
31			Br	Cl
32		H		H
33		H	Br	H
34				H
35			Br	
36		H		H
37		H		
38		H		H

39		H		H
40		H		H
41		H	Br	H
42		H		H
43		H		H
44		H		H
45		H		H
46		H		H
47		H		H
48		H		H
49		H		H
50		H	H	Cl

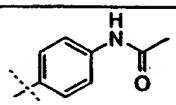
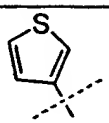
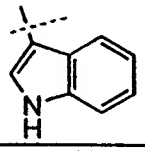
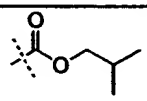
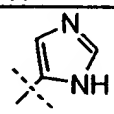
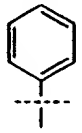
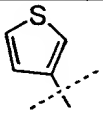
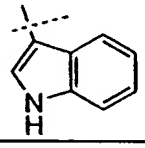
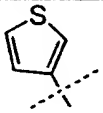
51		H		H
52		H		H
53		H		H
54		H		H
55		H		

Table 2

Compound	Name
1	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
2	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
3	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-vinyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
4	5-Acetyl-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
5	5-Bromo-3-(4-hydroxy-3,5-dinitro-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
6	5-Bromo-3-(3,5-dichloro-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
7	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
8	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-3-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
9	4-[3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzenesulfonamide
10	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenylethynyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
11	5-[3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl]-nicotinamide
12	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid benzyl ester
13	Isopropyl-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-2-oxo-1,2-dihydro-3*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate

14	5-(2-Bromoacetyl)-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
15	3-(3,5-dibromo-4-hydroxy-benzylidene)-5-(2-methyl-thiazol-4-yl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
16	5-(2-Amino-thiazol-4-yl)-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
17	5-Bromo-3-quinolin-3-ylmethylene-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
18	5-Bromo-3-[4-(2-hydroxy-ethoxy)-benzylidene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
19	5-(5-Bromo-2-oxo-1,2-dihydro-pyrrolo[2,3-b]pyridin--3-ylidenemethyl)benzoic acid
20	5-Bromo-3-[1-(3,5-dichlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
21	5-Bromo-3-[1-(4-chlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
22	3-(3,5-Dibromo-4-hydroxybenzylidene)-5-ethyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
23	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenethyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
24	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid isobutyl ester
25	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester
26	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester
27	3-(3-Bromo-4-hydroxy-5-(2'-methoxyphenyl)-benzyl-idene)-5-bromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

Table 2A	
Compound	Name
28	5-Bromo-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
29	5-Bromo-3-[(3-phenoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
30	6-chloro-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1*H*-pyrrolo[2,3-*b*]pyridin-2-one
31	5-Bromo-6-chloro-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
32	3-[((3-Fluorophenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
33	5-bromo-3-[3,5-difluorophenyl)methylidene]-1*H*-pyrrolo[2,3-*b*]pyridin-2-one
34	3-[(2,3-Dibromo-4-hydroxy-5-methoxyphenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
35	5-bromo-3-[(3,5-dimethyl-1*H*-pyrrol-2-yl)methylidene]-1*H*-pyrrolo[2,3-*b*]pyridin-2-one
36	4-(5-{[2-Oxo-5-(3-thienyl)-1,2-dihydro-3H-pyrrolo[2,3-b]pyridin-3-ylidene]methyl}-2-furyl)benzenesulfonamide
37	3-[2-Furylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one
38	3-(4-[3-(dimethylamino)propoxy]phenylmethylidene)-5-(3-thienyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-one
39	5-(3-thienyl)-3-[2-thienylmethylidene]-1*H*-pyrrolo[2,3-*b*]pyridin-2-one
40	3-[3,5-dimethyl-1*H*-pyrrol-2-yl)methylidene]-5-(3-thienyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-one
41	5-Bromo-3-[(4-hydroxy-3,5-diisopropylphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-

	one
42	3-[(4-Hydroxy-2-methoxyphenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
43	Isopropyl 3-{[4-hydroxy-3-(hydroxymethyl)phenyl]methylidene}-2-oxo-1,2-dihydro-3H-pyrrolo[2,3-b]pyridine-5-carboxylate
44	3-[(3,5-Dibromo-4-hydroxyphenyl)methylidene]-5-(3-pyridinyl)-1H-pyrrolo[2,3-b]pyridin-2-one
45	3-[(3,5-Dichloro-4-hydroxyphenyl)methylidene]-5-(2-furyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one
46	3-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylidene]-5-(2-furyl)-1H-pyrrolo[2,3-b]pyridin-2-one
47	5-(2-Furyl)-3-[(4-hydroxy-2-methoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
48	3-({4-[3-(Dimethylamino)propoxy]phenyl}methylidene)-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
49	3-[(2,6-Difluorophenyl)methylidene]-5-(3-thienyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one
50	6-Chloro-3-({4-[3-(dimethylamino)propoxy]phenyl}-methylidene)-1H-pyrrolo[2,3-b]pyridin-2-one
51	N-(4-{[2-Oxo-5-(3-thienyl)-1,2-dihydro-3H-pyrrolo[2,3-b]pyridin-3-ylidene]methyl}phenyl)acetamide
52	Isobutyl 2-oxo-3-[(2-pyridinylmethylidene]-1,2-dihydro-3H-pyrrolo[2,3-b]pyridine-5-carboxylate
53	3-[1H-Imidazol-4-ylmethylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
54	3-[Phenylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one
55	3-[1H-Indol-3-ylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Aluminum, Benzenesulfonate, Benzoate,

Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium, Calcium Edetate, Camsylate, Carbonate, Chloride, Chloroprocaine, Choline, Clavulanate, Citrate, Dibenzylethylenediamine, Diethanolamine, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Ethylenediamine, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lithium, Lactobionate, Laurate, Malate, Maleate, Magnesium, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Procaine, Salicylate, Sodium, Stearate, Subacetate, Succinate, Sulfate, Tannate, Tartrate, Teoclate, Tosylate, Triethanolamine, Triethiodide, Trimethylammonium and Valerate.

Salts which are not pharmaceutically acceptable may be useful in the preparation of intermediates towards the final synthesis of compounds of formula (I) and these form a further aspect of the invention.

Also included within the scope of the invention are the individual chiral isomers of the compounds represented by formula (I) above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

For the following defined terms, these definitions shall be applied, unless a different definition is given in the claims or elsewhere in this specification.

As used herein, the term "aliphatic" refers to the terms alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene, as those terms are defined below.

As used herein, the term "lower" refers to a group having between one and six carbons, unless specified or implied otherwise in the text.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having a specified number of carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include , but are not limited to, n-butyl, n-pentyl, isobutyl, and isopropyl, and the like. The term "alkyl" as used herein also generically refers to the below-defined terms, "alkylene", "alkenyl", "alkenylene", "alkynyl" and "alkynylene".

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

As used herein, the term "alkenyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon double bond, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed.

As used herein, the term "alkenylene" refers to an straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon double bonds, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed or others as identified throughout this specification and claims. Examples of "alkenylene" as used herein include, but are not limited to, ethene-1,2-diyl, propene-1,3-diyl, methylene-diyl, and the like.

As used herein, the term "alkynyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon triple bond, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by substituents such as alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed.

As used herein, the term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon triple bonds, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "alkynylene" as used herein include, but are not limited to, ethyne-1,2-diyl, propyne-1,3-diyl, and the like.

As used herein, "cycloalkyl" refers to an alicyclic hydrocarbon group with one or more degrees of unsaturation, having from three to twelve carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and the like. The term"cycloalkyl" as used herein also generically refers to the below defined terms "cycloalkylene", "cycloalkenyl", and "cycloalkenylene".

As used herein, the term "cycloalkylene" refers to an non-aromatic alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "cycloalkenyl" refers to a substituted alicyclic hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower

perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 1-cyclopentene-3-yl, 1-cyclohexene-3-yl, 1-cycloheptene-4-yl, and the like.

As used herein, the term "cycloalkenylene" refers to a substituted alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 4,5-cyclopentene-1,3-diyl, 3,4-cyclohexene-1,1-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO_2, O, or N, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like. A more comprehensive listing of such rings is found in the Summary of the Invention.

The term "heterocyclic" also generically refers to the below-defined terms "heterocyclylene", "heteroaryl", and "heteroarylene" .

As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO_2, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, or others as identified throughout this specification and claims or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like. A more comprehensive listing of such rings is found in the Summary of the Invention.

As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, which is referred to herein as a "biaryl", optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, and the like.

As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "heteroaryl" refers to a five - to seven - membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or others identified throughout this specification and claims, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole, and the like. A more comprehensive listing of such rings is found in the Summary of the Invention.

The term "heteroaryl" also generically refers to the below-defined term "heteroarylene".

As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" refers to the group R_aO-, where R_a is alkyl, alkenyl or alkynyl.

As used herein, the term "alkylsulfanyl" refers to the group R_aS-, where R_a is alkyl, alkenyl, or alkynyl.

As used herein, the term "alkenylsulfanyl" refers to the group R_aS-, where R_a is alkenyl or alkynyl.

As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)$-, where R_a is alkyl, alkenyl or alkynyl.

As used herein, the term "alkylsulfonyl" refers to the group R_aSO_2-, where R_a is alkyl, alkenyl or alkynyl.

As used herein, the term "acyl" refers to the group $R_aC(O)$- , where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyl" refers to the group $R_aC(O)$- , where R_a is aryl.

As used herein, the term "heteroaroyl" refers to the group $R_aC(O)$- , where R_a is heteroaryl.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)$-, where R_a is alkyl.

As used herein, the term "carbamate" or "carbamoyl" refers to the group $R_aR_bNC(O)$-, where R_a and R_b are hydrogen, alkyl, aryl, heterocyclyl or heteroaryl.

As used herein, the term "alkylcarbonyloxy" refers to the group $R_aC(O)O$- , where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyloxy" refers to the group $R_aC(O)O$- , where R_a is aryl.

As used herein, the term "heteroaroyloxy" refers to the group $R_aC(O)O$- , where R_a is heteroaryl.

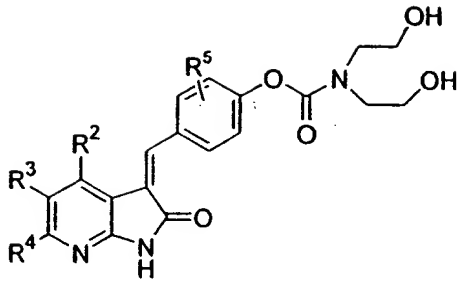
From time to time in this specification and claims, the term "optionally" appears, followed by recitation of one or more chemical substitutions or reactions. As used herein, the term "optionally" means that the subsequently described substitution or reaction(s) may or may not occur at the option of one of ordinary skill in the art conducting the substitution or reaction, and includes both those situations where the substitution or reaction has occurred and those where it has not occurred.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed.

As used herein, the terms "bears" or "bearing" can refer to in-line insertion substitutions at any position along the above-defined aliphatic, alkyl, alkenyl, alkynyl or cycloalkyl substituents' chain lengths, with one or more of any of -O-, -S-, -S(O)-, $-S(O)_2-$, -N(H)-, or -N(aliphatic)-, including, for example, $-CH_2-O-CH_2-$, $-CH_2-SO_2-CH_2-$, $-CH_2-NH-CH_3$ and so forth.

As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or acetic acid.

As used herein, the terms "biohydrolyzable carbamate" , "biohydrolyzable carbonate" and "biohydrolyzable ureide" is a carbamate, carbonate or ureide, respectively, of a drug substance (in this invention, a compound of general formula (I) which either: a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as uptake, duration of action, onset of action, and the like; or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable carbamate is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art, and include by way of example carbamates of lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, polyether amines, and the like. An example of such a biohydrolyzable carbamate applied to the general formula (I) is illustrated below in general formula (A)



(A)

Other examples of biohydrolyzable carbamates include those situations in which R^5 is an OH moiety and said OH is conjugated with a carbamoyl conjugate to yield a biohydrolyzable carbamate wherein said carbamoyl conjugate is selected from the group consisting of diethylaminocarbonyl, N-(2-hydroxyethyl)aminocarbonyl, N,N,-bis(2-hydroxyethyl)aminocarbonyl, 4-morpholinocarbonyl and 4-methyl-1-piperazinylcarbonyl.

As used herein, the term "biohydrolyzable ester" is an ester of a drug substance (in this invention, a compound of general formula (I) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable ester is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl esters, lower acyloxy-alkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

As used herein, the term "biohydrolyzable amide" is an amide of a drug substance (in this invention, a compound of general formula (I) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable amide is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

As used herein, the term "prodrug" includes biohydrolyzable amides and biohydrolyzable esters and biohydrolyzable carbamates, carbonates, and ureides, and also encompasses: a) compounds in which the biohydrolyzable functionality in such a prodrug is encompassed in the compound of formula (I), for example, the lactam formed by a carboxylic group in R^2 and an amine in R^3; and b) compounds which may be oxidized or reduced biologically at a given functional group to yield drug substances of formula (I). Examples of these functional groups are, but are not limited to, 1,4-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

As used herein, the term "hydrate" means a crystalline substance containing one or more molecules of water of crystallization.

As used herein, the term "affinity reagent" is a group attached to the compound of formula (I) which does not affect its in vitro biological activity, allowing the compound to bind to a target, yet such a group binds strongly to a third component allowing: a) characterization of the target as to localization within a cell or other organism component, perhaps by visualization by fluorescence or radiography; or b) facile separation of the target from an unknown mixture of targets, whether proteinaceous or not proteinaceous. An example of an affinity

reagent according to criterion (b) would be biotin either directly attached to (I) or linked with a spacer of one to 50 atoms selected from the group consisting of C, H, O, N, S, or P in any combination. An example of an affinity reagent according to criterion (a) above would be fluorescein, either directly attached to (I) or linked with a spacer of one to 50 atoms selected from the group consisting of C, H, O, N, S, or P in any combination.

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. arylalkoxyaryloxy) they shall be interpreted as including those limitations given above for "aliphatic" and "aryl". Alkyl or cycloalkyl substituents shall be recognized as being functionally equivalent to those having one or more degrees of unsaturation. Designated numbers of carbon atoms (e.g. C_{1-10}) shall refer independently to the number of carbon atoms in an aliphatic or cycloaliphatic moiety or to the aliphatic portion of a larger substituent.

As used herein, the term "oxo" shall refer to the substituent =O.

As used herein, the term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

As used herein, the term "mercapto" shall refer to the substituent -SH.

As used herein, the term "carboxy" shall refer to the substituent -COOH.

As used herein, the term "cyano" shall refer to the substituent -CN.

As used herein, the term "aminosulfonyl" shall refer to the substituent $-SO_2NH_2$.

As used herein, the term "carbamoyl" shall refer to the substituent $-C(O)NH_2$.

As used herein, the term "sulfanyl" shall refer to the substituent -S-.

As used herein, the term "sulfenyl" shall refer to the substituent -S(O)-.

As used herein, the term "sulfonyl" shall refer to the substituent $-S(O)_2-$.

The compounds of formula (I) can be prepared readily according to the following reaction Schemes (in which all variables are as defined before) and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

Preparation

The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself describe a genus of the invention. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

Abbreviations used in the Examples are as follows:

g = grams
mg = milligrams
L = liters

mL = milliliters
mL =microliters
M = molar
N = normal
mM = millimolar
i.v. = intravenous
p.o. = per oral
s.c. = subcutaneous
Hz = hertz
mol = moles
mmol = millimoles
mbar = millibar
psi = pounds per square inch
rt = room temperature
min = minutes
hr = hours
mp = melting point
TLC = thin layer chromatography
R_f = relative TLC mobility
MS = mass spectrometry
NMR = nuclear magnetic resonance spectroscopy
APCI = atmospheric pressure chemical ionization
ESI = electrospray ionization
m/z = mass to charge ratio
HPLC = high pressure liquid chromatography
t_r = retention time
Pd/C = palladium on activated carbon
ether = diethyl ether
MeOH = methanol
EtOAc = ethyl acetate
TEA = triethylamine
DIEA = diisopropylethylamine

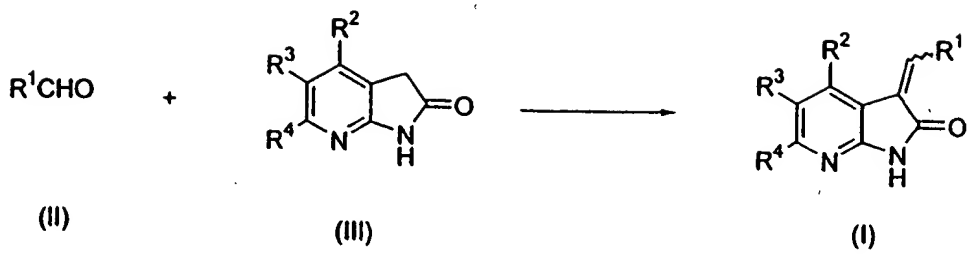
THF = tetrahydrofuran
DMF = N, N-dimethylformamide
DMSO = dimethylsulfoxide
DDQ =2,3-dichloro-5,6-dicyano-1,4-benzoquinone
LAH = lithium aluminum hydride
TFA = trifluoroacetic acid
HCl = hydrochloric acid
LDA = lithium diisopropylamide
THP = tetrahydropyranyl
NMM = N-methylmorpholine, 4-methylmorpholine
HMPA= hexamethylphosphoric triamide
DMPU= 1,3-dimethylpropylene urea
d = days
ppm = parts per million
kD = kiloDalton
LPS = lipopolysaccharide
PMA = phorbol myristate acetate
SPA = scintillation proximity assay
EDTA = ethylenediamine tetraacetic acid
FBS = fetal bovine serum
PBS = phosphate buffered saline solution

Several of the following examples represent single E isomers, single Z isomers and mixtures of E/Z isomers. Determination of the E and Z isomers can be done by analytical methods such as x-ray crystallography, ^{1}H NMR and ^{13}C NMR.

GENERAL REACTION SCHEMES

Compounds of the invention may be prepared by methods known in the art, where such a method is shown in the Reaction Schemes shown below.

Reaction Scheme 1

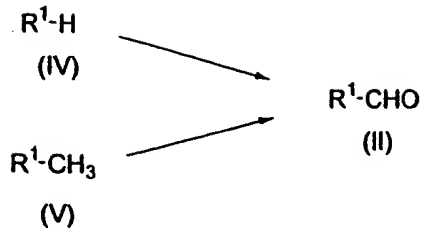


R^1, R^2, R^3, R^4 are defined as above for formula (I).

The conversion of (II) and (III) to (I) involves methods known as the aldol condensation followed by elimination which is well described in "Advanced Organic Chemistry," Carey and Sundberg, 3rd edition, Plenum Press, 1990, principally contained in chapter 2 of part B. The reaction may be conducted using acid (for example concentrated HCl) in combination with a suitable solvent, such as acetic acid at temperatures ranging from 25 °C to 150 °C. Lewis acid or catalytic acid conditions may also be used such as a catalytic amount of para-toluenesulfonic acid or boron trifloride etherate in a suitable solvent such as toluene at temperatures ranging from 25 °C to 125°C. Alternatively, basic conditions may be applied to effect an aldol/elimination reaction such as treatment with sodium hydride in a suitable sovent such as THF at temperatures ranging from -20 °C to 22 °C or treatment with pyrrolidine in ethyl alcohol at temperatures ranging from 25 °C to 80 °C. Some of these compounds of formula (I) may also be synthesized according to Reaction Scheme 1 by combining (II) and (III) in a suitable solvent such as toluene and heating at temperatures ranging from 40 °C to 125 °C for 1h to 7 days.

Aromatic, heterocyclic and heteroaromatic aldehydes of formula (II) are commercially available, or may be prepared by published procedures. Reaction Scheme 2 depicts two routes to readily synthesize substituted aromatic and heteroaromatic aldehydes that are not commercially available.

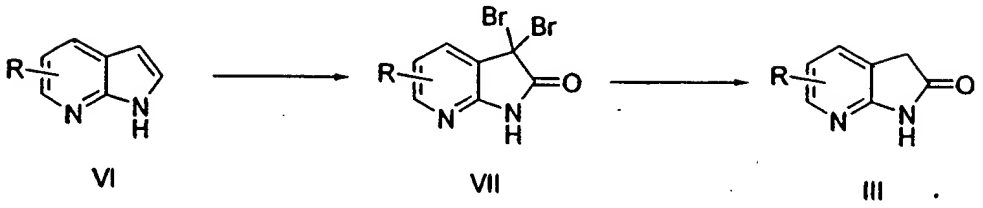
Reaction Scheme 2



Generation of the substituted compounds of formula (II) may be obtained by a variety of methods by those skilled in the art. For example, the conversion of (IV) to (II) may be conducted by treating (IV) in a suitable solvent such as acetic acid with hexamethylenetetramine at a temperature of 90 °C to 130 °C. Preparation of the proper aldehydes may also be achieved via a well known Vilsmeier-Haak reaction (A. Vilsmeier, A. Haak, *Beriche*, 60, 119, 1927) wherein the formylation of aromatic or heteroaromatic compounds may be achieved by treatment with disubstituted formamide, such as *N,N*-dimethylformamide, and phosphorus oxychloride. Alternatively, (V) can be converted to (II) by treating (V) in a suitable solvent such as dioxane with reagents capable of oxidation, for example with a small amount of water with DDQ at a temperature of 0 °C to 140 °C. In addition to the above, one compound of formula (II) can be converted to another compound of formula (II) by a chemical transformation of the appropriate substituent or substituents. For example, when R^1 is substituted with an hydroxyl in (II), the conversion to a carbamate, carbonate, and ether is conducted by treating (II) in a suitable solvent such as THF with an alkylating agent such as chloromethyl-R, or an acylating agent such as alkylchloroformates and alkylcarbamoylchlorides in a suitable solvent such as dichloromethane.

7-aza-oxindoles of formula (III) may be prepared by published procedures or variations of published procedures. Reaction Scheme 3 depicts a route to synthesize compounds of formula (III)

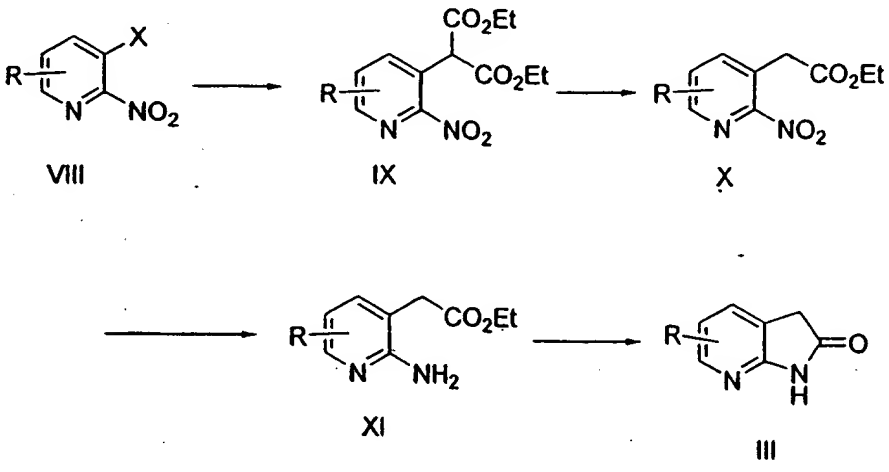
Reaction Scheme 3



VI VII III

A pyrrolopyridine of formula (VI) may be converted to (VII) utilizing a method well described in the literature (A. Marfat and M. Carta, *Tetrahedron letters*, 28(35) pp 4027-4030, 1987) by treatment with pyridinium perbromide in a suitable solvent such as t-butyl alcohol at a temperature of 25 °C. A compound of formula (VII) may be converted to (III) by treatment with 10 % Pd/C in a suitable solvent such as anhydrous ethanol at 30 to 50 psi of hydrogen or by treatment with a saturated solution of ammonium chloride followed by treatment with activated zinc in a suitable solvent such as THF.

Reaction Scheme 4

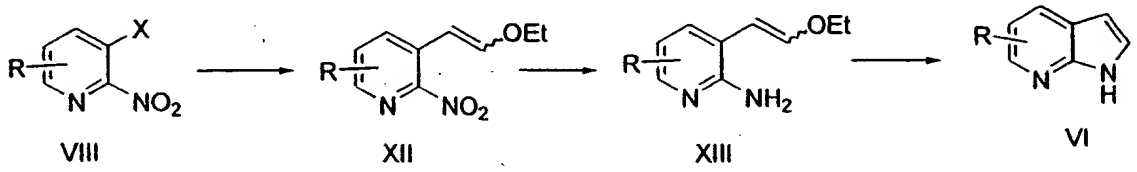


VIII IX X XI III

An alternative route to synthesize appropriately substituted 7-aza-oxindoles of formula III is depicted in Reaction Scheme 4 beginning with substituted pyridines. For example, where X is chlorine in compound VIII, the conversion of VIII to IX

may be conducted by treatment with the anion of diethyl malonate such as that prepared by treatment of diethyl malonate in a suitable solvent such as dimethylsulfoxide with sodium hydride. The decarboxylation of IX to obtain X may be conducted by heating IX in wet dimethyl sulfoxide containing a simple salt, such as lithium chloride which is well know in the literature (Krapcho, Synthesis, 805-822, 1982 or for another method Aneja, Hollis, Davies, Eaton, Tetrahedron Letters, 24, 4641, 1983). The conversion of X to XI may be conducted using a metal catalyst capable of reducing nitro groups to amino groups such as palladium on carbon in a suitable solvent such as ethanol under an atmosphere of hydrogen gas.

Reaction Scheme 5



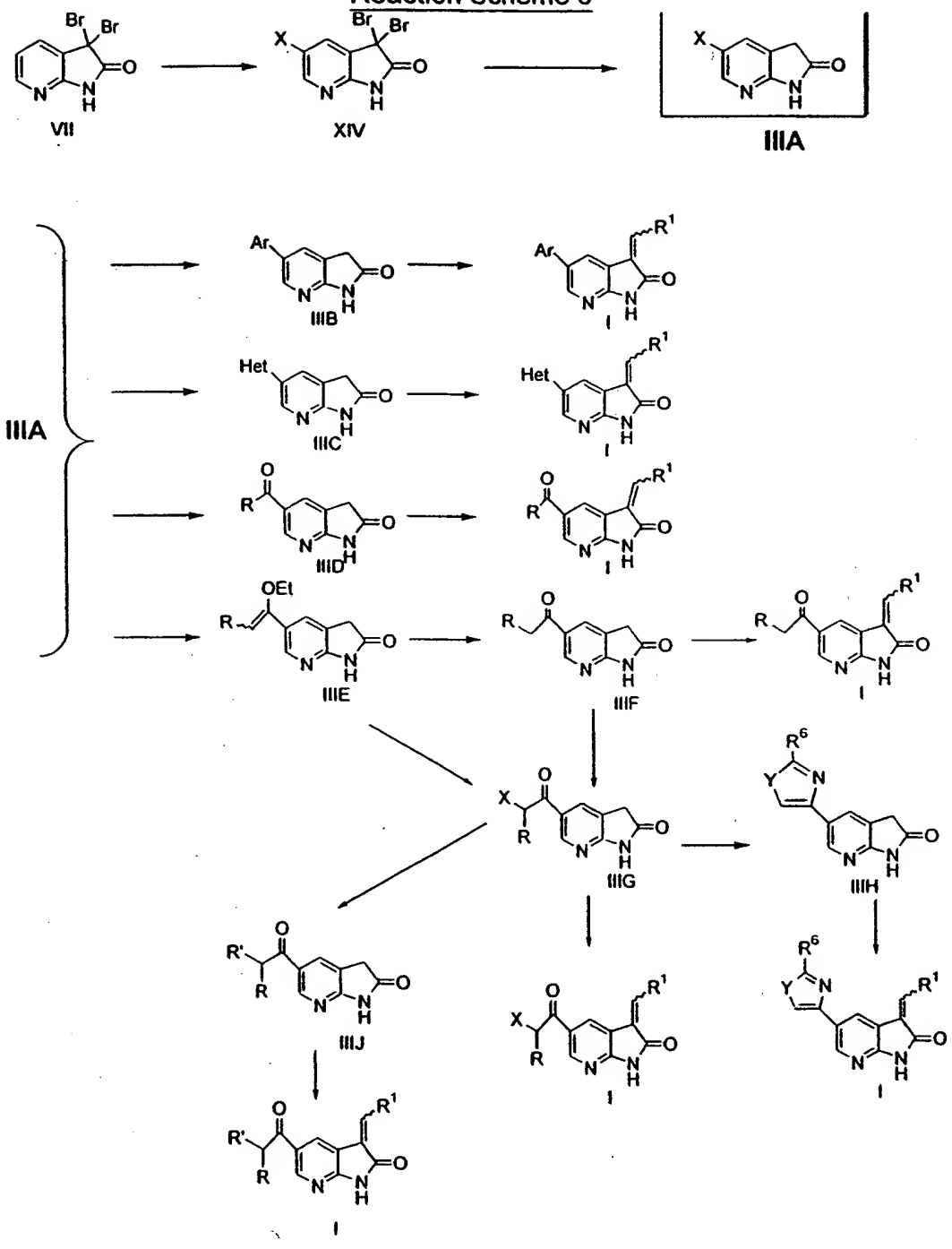
VIII XII XIII VI

The syntheses of variously substituted pyrrolopyridines (VI) are well described in the literature (for example: T. Sakamoto, C. Satoh, Y. Kondo, H. Yamanaka Heterocycles 1992, 34(12), 2379-2384 and references cited therein). Reaction Scheme 5 depicts one convenient method that begins with commercially available pyridines VIII. The 2-ethoxyethenyl group may be introduced by a palladium-catalyzed reaction, for example, in the conversion of VIII to XII, by treatment of the pyridine derivative VIII with 1-ethoxy-2-tributylstannylethene and a palladium catalyst such as dichlorobis(triphenylphosphine)palladium(II) in a suitable solvent such as acetonitrile. A catalytic hydrogenation of XII may be conducted to obtain XIII under typical conditions such as treatment of XII with a metal catalyst capable of reducing a nitro group to an amino group such as W-2 Raney Nickel in a suitable solvent such as methanol under an atmosphere of hydrogen. The cyclization of XIII to a substituted pyrrolopyridine (VI) may be conducted utilizing

acidic conditions such as treatment of XIII with concentrated hydrochloric acid in a suitable solvent such as methanol at temperatures ranging from 0 °C to 100 °C.

In addition to incorporating substitutions into the initial stages of the synthesis, one compound of formula (III) can be converted to another compound of formula (III) by a chemical transformation to the appropriate substituent or substituents. For example, Reaction Scheme 6 depicts several well established transformations for the functionalization of a halogenated 7-aza-oxindole of formula (III) which, while demonstrated for a 5-position halogen, is not limited to that position.

Reaction Scheme 6



By utilizing intermediate VII (from Reaction Scheme 3), an appropriately halogenated 7-azaoxindole may be obtained via intermediate XIV. Treatment of compounds of formula VII with bromine in the presence of aqueous sodium bicarbonate in a suitable solvent such as tertiary butyl alcohol to provide XIV may subsequently treated with a saturated aqueous solution of ammonium chloride and activated zinc dust to afford IIIA. Palladium catalyzed coupling of an iodo, bromo, or triflate functionalized reagent with the appropriately substituted organotin or boronate reagent will provide a broad range of the compounds of formula III. A compound of formula (IIIA) where X is bromo or iodo may be treated with a tributyltin heterocycle, for example 3-pyridyltributyltin, or a trialkyltin aryl compound such as 4-(tributyltin)benzene sulfonamide in the presence of a palladium catalyst, for example bistriphenylphosphine dichloropalladium, in a suitable solvent, such as acetonitrile, to form (IIIB or IIIC). Alternately, (IIIA) may be converted to (IIIB or IIIC) by treatment with a heterocyclic or aromatic boronic acid, for example thiophene-3-boronic acid, in the presence of base, for example tetrakis-triphenyl phosphine palladium, in a suitable solvent, such as toluene, at a temperature of 22°C to 125°C. Similarly, where X is a hydroxyl group, it may first be converted to a triflate through standard conditions such as treatment with trifluoromethanesulfonic anhydride in the presence of a base such as sodium hydride in a suitable solvent such as benzene before the aforementioned chemistry is applied. It may be appreciated by one skilled in the art that such coupling reactions may be conducted through the alternative coupling partners in order to obtain compounds such as IIIB and IIIC. For example, the organotin or boron component may reside on the pyrrolopyridinone partner and the halogen or triflate on the aryl or heteroaromatic partner.

The conversion of IIIA to IIID where R is a lower alkoxy group may be conducted through a palladium mediated carbonylation reaction. This reaction may be carried out in a Parr shaker apparatus by treatment of IIIA with a lower alky alcohol such as ethanol in a suitable solvent such as dimethylsulfoxide in the presence of a palladium catalyst such as palladium diacetate and a suitable base such as triethylamine under an atmosphere of carbon monoxide gas. When R is

OH in IIID which can be synthesized in an analogous method as that described for the ester, the conversion of carboxylic acid IIID to esters and amides of formula IIID involves methods known in peptide chemistry, for example the reaction may be conducted using HOBt in combination with a dehydrating agent such as dicyclohexylcarbodiimide in a suitable solvent such as DMF. The conversion of IIIA to IIIF may be obtained through intermediate IIIE via a palladium catalyzed tin coupling reaction.

The conversion of IIIA to IIIE may be achieved by treatment of IIIA with a trialkyl(alkoxyvinyl)tin reagent such as tributyl(1-ethoxyvinyl)tin in the presence of a palladium catalyst such as dichlorobis(triphenylphosphine)palladium(II) in a suitable solvent such as acetonitrile. To obtain IIIF, IIIE may be treated with acid such as hydrochloric acid in a suitable solvent such as diethylether. Either IIIE or IIIF may be converted to a halomethyl ketone of formula IIIG by treatment with a halogenating reagent such as *N*-halosuccinimide in the presence of water in a suitable solvent such as tetrahydrofuran. Further functionalization to various heterocyclic groups may be achieved through treatment of IIIG with diversely substituted amidines, thioamides, ureas and substituted aminopyridines. For example, IIIG may be converted to IIIH by treating IIIG with thioacetamide in a suitable solvent such as acetic acid at a temperature of 22 °C to 100 °C. Compounds of formula IIIJ, where R' is, for example an alkyl or cyclic amine, may be obtained by treatingIIIG with diverse nucleophiles such as amines in a suitable solvent such as THF at a temperature of 22 °C to 80 °C. These functionalized 7-aza-oxindoles (for example, IIIA, IIIB, IIIC, IIID, IIIF, IIIG, IIIH and IIIJ) may be converted to a compound of formula I using previously described chemistry.

PHARMACEUTICAL FORMULATION AND DOSES

The compounds of the present invention can be administered in such oral (including buccal and sublingual) dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous

(both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

A therapeutically effective amount of a compound or salt of the present invention will depend upon a number of factors including, for example, the age and weight of the animal or patient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.1 to 300 mg/kg of body weight per day, and particularly 1 to 100 mg/kg of body weight per day. Oral dosage units will generally be administered in the range of from 1 to about 250 mg and more preferably from about 25 to 250 mg. The daily dosage for a 70 kg mammal will generally be in the range of about 10 mg to 5 grams of a compound of formula I. An effective amount of a salt of the present invention may be determined as a proportion of the effective amount of the compound per se.

Topical application similarly may be once or more than once per day depending upon the usual medical considerations. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered

in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or

sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl

alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

Parenteral administration can be effected by utilizing liquid dosage unit forms such as sterile solutions and suspensions intended for subcutaneous,

intramuscular or intravenous injection. These are prepared by suspending or dissolving a measured amount of the compound in a non-toxic liquid vehicle suitable for injection such as aqueous oleaginous medium and sterilizing the suspension or solution.

Alternatively, a measured amount of the compound is placed in a vial and the vial and its contents are sterilized and sealed. An accompanying vial or vehicle can be provided for mixing prior to administration. Non-toxic salts and salt solutions can be added to render the injection isotonic. Stabilizers, preservations and emulsifiers can also be added.

Rectal administration can be effected utilizing suppositories in which the compound is admixed with low-melting water-soluble or insoluble solids such as polyethylene glycol, cocoa butter, higher ester as for example flavored aqueous solution, while elixirs are prepared through myristyl palmitate or mixtures thereof.

Topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g.

gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

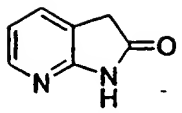
The preferred pharmaceutical compositions are those in a form suitable for oral administration, such as tablets and liquids and the like and topical formulations.

SYNTHESIS EXAMPLES

We now set forth a selected number of synthesis examples which illustrate the techniques used to obtain the compounds of the invention. It is believed that one of ordinary skill in the art will, in view of the synthesis schemes set forth above, be able to follow these procedures or modify them accordingly without undue experimentation in order to obtain any of the substitutions disclosed above. The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature. Example numbers refer to those compounds listed in the tables above. ^{1}H NMR spectra were obtained on VARIAN Unity Plus NMR spectrophotometers at 300 or 400 Mhz. Mass spectra were obtained on Micromass Platform II mass spectrometers from Micromass Ltd. Altrincham, UK, using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI). Analytical thin layer chromatography (TLC) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterization, and to follow the progress of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica gel 60 (230-400 mesh), and the stated solvent system under pressure.

Methods for the synthesis of compounds of formula (III):

Example of Method A:



7-Azaoxindole

a) 3,3-Dibromo-7-azaoxindole

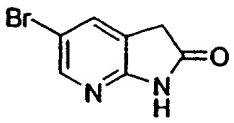
A solution of 7-azaindole (4.0g, 34 mmol) in tert-BuOH (200 mL) is stirred at room temperature and pyridinium perbromide (32.5g, 0.1 mol) is added in portions over 30 min. and the reaction mixture is stirred for 3 h. Pyridinium perbromide (10.8 g, 33 mmol) is added and the mixture is stirred for a further 2 h. The tert-BuOH is evaporated under educed pressure and the residue is partitioned between water (300 mL) and EtOAc (300 mL). The organic layer is separated and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with water (2 x 50 mL), and brine. The organic layer is dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. Trituration of the residue with CH_2Cl_2 gives a white solid which is collected by filtration and dried under vacuum to give 3,3-dibromo-7-azaoxindole, 8.35g. ^1H NMR (d^6 DMSO) δ 11.99 (s, 1H), 8.21 (dd, 1H, J = 5.1, 1.5 Hz), 8.00 (dd, 1H, J = 7.5, 1.5 Hz), 7.17 (dd, 1H, J = 7.5, 5.1 Hz). MS (+ve ES) 293 (28), (M+H), 147 (100).

b) 7-Azaoxindole

A solution of 3,3-dibromo-7-azaoxindole (2.0g, 7.2 mmol) in THF (50 mL) is stirred at room temperature and a saturated aqueous solution of NH_4Cl is added. Activated zinc powder is added and the reaction mixture is stirred for 2 h. The zinc is removed by filtration through a pad of diatomaceous earth and the organic layer is separated. The aqueous layer is extracted with THF (10 mL) and the combined organic layers are dried over anhydrous $MgSO_4$, filtered and evaporated. The residue is slurried in 10:1 $CHCl_3$:MeOH (15 mL) and filtered through a pad of silica gel and the filtrate is evaporated. The residue is triturated with water and the solid is collected by filtration and dried under vacuum to give 7-azaoxindole, 0.668g (70%). ^1H NMR (d^6 DMSO) δ 10.94 (s, 1H), 8.02 (d, 1H, J =

5.2 Hz), 7.52 (d, 1H, J = 6.8 Hz), 6.90 (dd, 1H, J = 6.8, 5.2 Hz), 3.53 (s, 2H). MS(AP-ve) 133 (100) (M-H)

Example of Method B:



5 Bromo-7-azaoxindole

a) 3,3,5 Tribromooxindole

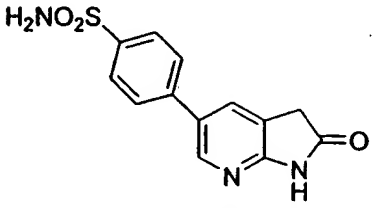
A solution of 3,3-dibromo-7-azaoxindole (5.0 g, 13.4 mmol) in tert-BuOH (100 mL) and water (100 mL) is stirred at room temperature and bromine (5.5 g, 34.3 mmol) is added dropwise over 20 min. A saturated aqueous solution of sodium bicarbonate (approx. 15 mL) is added dropwise over 30 min to raise the pH of the solution to 6.5. The yellow solid formed is collected by filtration. The filtrate is condensed to approx. 100 mL and extracted with $CHCl_3$ (2 x 50 mL). The combined organic extracts are dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure to leave a yellow solid. The solids are combined and dried under vacuum to give 3,3,5 tribromooxindole as a yellow solid, 6.25 g (98%). ^1H NMR ($CDCl_3$) δ 9.4 (br s, 1H), 8.28 (d, 1H, J = 2 Hz), 7.95 (d, 1H, J = 2 Hz).

b) 5 Bromo-7-azaoxindole

A solution of 3,3,5 tribromooxindole (5.0 g, 13.4 mmol) in fresh THF (100 mL) is stirred at room temperature and a saturated aqueous solution of ammonium chloride (100 mL) is added. The flask is placed in a water bath and activated zinc dust (15.0 g, 230 mmol) is added. The mixture is stirred for 20 min and the zinc is removed by filtration through a pad of diatomaceous earth. The organic layer is seperated and the aqueous layer is extracted with THF (20 mL). The combined organic layers were washed with saturated brine solution, dried over anhydrous amgnesium sulfate and the solvent removed under reduced

pressure. The brown residue is triturated with water (20 mL) and the tan solid is collected by filtration and dried under vacuum to give 5-bromo-7-azaoxindole as a tan solid, 2.02 g (71%). ^{1}H NMR (d^6 DMSO) δ 11.13 (s, 1H), 8.15 (s, 1H), 8.76 (s, 1H), 3.57 (s, 2H). MS (AP -ve) 211 (100) (M-H).

Example of Method C:



5-(4-benzenesulfonamide)-7-azaoxindole

a) 4-(tributyltin) benzenesulfonamide

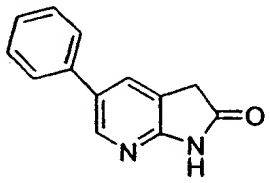
A mixture of 1 g (4.2 mmol) of 4-bromo benzene sulfonamide, 3.65 g (6.3 mmol) of bis(tributyltin), and 0.046 g (0.04 mmol) of palladium tetrakis triphenylphosphine in 25 ml of acetonitrile and 3 ml of toluene was heated to reflux for 18 hrs. After cooling to ambient temperature the reaction mixture was diluted with EtOAc and the excess bis(tributyltin) was removed via separatory funnel. The solvent was removed *in vacuo,* and the residue was chromatographed on silica gel (Hex/EtOAc 2:1) to afford 4-tributyltin benzene sulfonamide as white solid (0.97 g, 52%): ^{1}H NMR (DMSO-d$_6$): d 0.81 (t, J = 7.32 Hz, 9H), 1.02-1.08 (m, 6H), 1.20-1.30 (m, 6H), 1.42-1.52 (m, 6H), 7.27 (s, 2H), 7.60 (d, J = 7.87 Hz, 2H), 7.72 (d, J = 7.87 Hz, 2H).

b) 5-(4-benzenesulfonamide)-7-azaoxindole

A mixture of 0.446 g (1 mmol) of 4-tributyltin benzene sulfonamide, 0.426 g (2 mmol) of 5-bromo-7-aza-oxindole, 0.497 g (3 mmol) of tetraethyl ammonium chloride, and 0.070 g (0.1 mmol) of bis(triphenylphospine) palladium (II) chloride in 20 ml of acetonitrile was heated to reflux for 48 hrs. After cooling to ambient temperature the solvent was removed *in vacuo,* and the residue was chromatographed on silica gel (EtOAc) to afford 4-(2-Oxo-2,3-dihydro-1H-

pyrrolo[2,3-b]pyridin-5-yl) benzenesulfonamide as white solid (0.85 g, 29%): ^{1}H NMR (DMSO-d_6): δ 3.60 (s, 2H), 7.36 (s, 2H), 7.81 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 2 Hz, 1H), 8.41 (d, J = 2 Hz, 1H), 11.12 (s, 1H); ESI-MS: *m/z* 290 $(m+H)^+$.

Example of Method D:

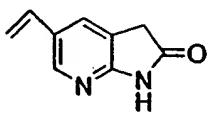


5-phenyl-7-azaoxindole

a) 5-phenyl-7-azaoxindole

To a stirred mixture of 5-bromo-7-azaoxindole (213 mg, 1 mmol) and phenylboronic acid (183 mg, 1.5 mmol) in toluene (6 ml) and ethanol (6 ml) were added 1 M sodium carbonate solution (2.5 ml, 2.5 mmol), lithium chloride (127 mg, 3 mmol) and dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol) under N_2 atmosphere. The reaction mixture was heated to reflux at 95 °C for 18 hours. The reaction mixture was diluted with chloroform (50 ml) and washed with brine (20 ml). The aqueous layer was thoroughly extracted with chloroform. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with diethyl ether yielded 5-phenyl-7-azaoxindole as a yellow solid (108 mg, 51.4%). ^{1}H NMR (d^6 DMSO): δ 11.04 (s, 1H), 8.32 (s, 1H), 7.83 (s, 1H), 7.60 (d, 2H, *J* = 7.4 Hz), 7.44 (t, 2H, *J* = 7.4 Hz), 7.32 (t, 1H, *J* = 7.4 Hz), 3.58 (s, 2H). MS (-ve APCI): 210 (48, M^+), 209 (100, M-H).

Example of Method E:

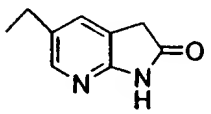


5-vinyl-7-azaoxindole

a) 5-vinyl-7-azaoxindole

To a stirred mixture of 5-bromo-7-azaoxindole (426 mg, 2 mmol) in acetonitrile (7 ml) were added tributyl(vinyl)tin (0.7 ml, 2.4 mmol), tetraethylammonium chloride (331 mg, 2 mmol), and dichlorobis(triphenylphosphine)palladium(II) (70.3 mg, 0.1 mmol) under N_2 atmosphere. The reaction mixture was heated to reflux at 95 °C for 22 hours. The reaction mixture was diluted with diethyl ether (100 ml) and washed with 2 M potassium fluoride solution (20 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with diethyl ether yielded 5-vinyl-7-azaoxindole as a yellow solid (128 mg, 40%). ^{1}H NMR (d^6 DMSO): δ 11.05 (s, 1H), 8.08 (s, 1H), 7.80 (s, 1H), 6.70 (dd, 1H, *J* = 11.1 & 17.7 Hz), 5.79 (d, 1H, *J* = 17.7 Hz), 5.22 (d, 1H, *J* = 11.1 Hz), 3.57 (s, 2H). MS (-ve APCI): 159 (100, M-H).

Example of Method F:

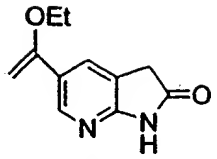


5-ethyl-7-azaoxindole

a) 5-ethyl-7-azaoxindole

To a stirred mixture of 5-vinyl-7-azaoxindole (32 mg, 0.2 mmol) in ethanol (10 ml) was added 10% palladium on carbon (10 mol %). Hydrogen (40 psi) was applied and the mixture was stirred at room temperature for 3 hours. The reaction mixture was filtered through celite and washed with ethanol. Evaporation of the filtrate under vacuum yielded 5-ethyl-7-azaoxindole as a peach solid (31 mg, 95.7%). ^{1}H NMR (d^6 DMSO): δ 10.92 (s, 1H), 7.91 (s, 1H), 7.47 (s, 1H), 3.54 (s, 2H), 2.56 (q, 2H, *J* = 7.4 Hz), 1.17 (t, 3H, *J* = 7.4 Hz). MS (-ve APCI): 161 (100, M-H).

Example of Method G:

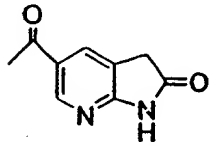


5-(1-ethoxyvinyl)-7-azaoxindole

a) 5-(1-ethoxyvinyl)-7-azaoxindole

To a stirred mixture of 5-bromo-7-azaoxindole (112 mg, 0.5 mmol) in acetonitrile (4 ml) were added tributyl(1-ethoxyvinyl)tin (228 mg, 0.6 mmol), tetraethylammonium chloride (174 mg, 1 mmol), and dichlorobis(triphenylphosphine)palladium(II) (37 mg, 0.05 mmol) under N_2 atmosphere. The reaction mixture was heated to reflux at 95 °C for 18 hours. The reaction mixture was diluted with diethyl ether (50 ml) and washed with 2 M potassium fluoride solution (10 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with diethyl ether yielded 5-(1-ethoxyvinyl)-7-azaoxindole as a yellow solid (59.5 mg, 55.4%). ^{1}H NMR (d^6 DMSO): δ 11.09 (s, 1H), 8.32 (s, 1H), 7.76 (s, 1H), 4.71 (s, 1H), 4.27 (s, 1H), 3.90 (q, 2H, J = 7 Hz), 3.58 (s, 2H), 1.36 (t, 3H, J = 7 Hz). MS (-ve APCI): 203 (38, M-H).

Example of Method H:



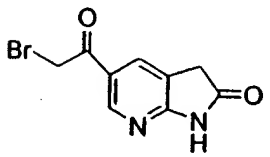
5-acetyl-7-azaoxindole

a) 5-acetyl-7-azaoxindole

To a stirred mixture of 5-bromo-7-azaoxindole (1 g, 4.69 mmol) in acetonitrile (30 ml) were added tributyl(1-ethoxyvinyl)tin (1.8 g, 4.93 mmol),

tetraethylammonium chloride (778 mg, 4.69 mmol), and dichlorobis(triphenylphosphine)palladium(II) (165 mg, 0.23 mmol) under N_2 atmosphere. The reaction mixture was heated to reflux at 95 °C for 15 hours. The reaction mixture was diluted with diethyl ether (100 ml) and washed with 2 M potassium fluoride solution (10 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with diethyl ether yielded 5-(1-ethoxyvinyl)-7-azaoxindole as a yellow solid (200 mg, 20.9%). The filtrate was evaporated to small volume and was purified by silica gel column chromatography, eluted with a gradient of ether in hexanes, to give 5-(methylcarbonyl)-7-azaoxindole as a yellow solid (203 mg, 24.5%). ^{1}H NMR (d_6-DMSO): δ 11.45 (s, 1H), 8.76 (s, 1H), 8.01 (s, 1H), 3.63 (s, 2H), 2.52 (s, 3H). MS (-ve APCI): 175 (100, M-H).

Example of Method I:

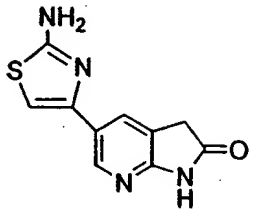


5-Bromomethylcarbonyl-7-azaoxindole

a) 5-(bromomethylcarbonyl)-7-azaoxindole

To a stirred solution of 5-(1-ethoxyvinyl)-7-azaoxindole (104 mg, 0.51 mmol) in tetrahydrofuran (12 ml) and water (1.2 ml) was added *N*-bromosuccinimide (109 mg, 0.61 mmol). The reaction mixture was stirred at room temperature for 5 min. The reaction mixture was diluted with ethyl acetate (50 ml), dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with dichloromethane/methanol yielded 5-(bromomethylcarbonyl)-7-azaoxindole as a tan solid (90.9 mg, 70%). ^{1}H NMR (d^6 DMSO): δ 11.53 (s, 1H), 8.82 (s, 1H), 8.05 (s, 1H), 4.90 (s, 2H), 3.67 (s, 2H). MS (-ve APCI): 255 (28, M^+).

Example of Method J:

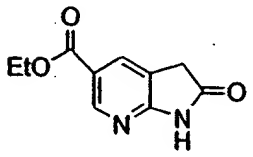


5-(2'-aminothiazole)-7-azaoxindole

a) 5-(2'-aminothiazole)-7-azaoxindole

To a stirred solution of 5-(bromomethylcarbonyl)-7-azaoxindole (90 mg, 0.35 mmol) in tetrahydrofuran (6 ml) was added thiourea (27 mg, 0.35 mmol). The reaction mixture was heated at 100 °C for 18 hours in sealed tube. The reaction mixture was filtered and washed with ethyl acetate. The filtrate was evaporated under vacuum to give crude product which was purified by preparative thin layer chromatography to give 5-(aminothiazole)-7-azaoxindole as a tan solid (32.2 mg, 39.3%). ^{1}H NMR (d^6 DMSO): δ 11.18 (s, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.60 (s, 1H), 7.10 (s, 1H), 3.63 (s, 2H). MS (-ve APCI): 231 (7, M-H).

Example of Method K:



5-carboethoxy-7-azaoxindole

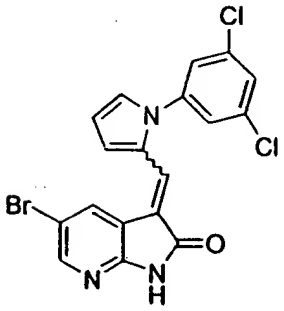
a) 5-carboethoxy-7-azaoxindole

To a mixture of 5-bromo-7-azaoxindole (213 mg, 1 mmol) in dimethylsulfoxide (1 ml) and ethanol (5 ml) in Parr bomb were added triethylamine (0.31 ml, 2.25 mmol), palladium acetate (33.7 mg, 0.15 mmol), and

1,4-(bisdiphenylphosphino)propane (61.9 mg, 0.15 mmol). Carbon monoxide gas (40 atm) was applied and the reaction mixture was heated at 95 °C for 18 hours with vigorously stirring. The reaction mixture was diluted with diethyl ether (50 ml) and washed with water (10 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with methanol yielded 5-(carboethoxy)-7-azaoxindole as a tan solid (53 mg, 25.7%). ^1H NMR (d^6 DMSO): δ 11.39 (s, 1H), 8.62 (s, 1H), 7.95 (s, 1H), 4.27 (q, 2H, *J* = 7 Hz), 3.59 (s, 2H), 1.28 (t, 3H, *J* = 7 Hz). MS (-ve APCI): 205 (4, M-H).

Methods for the synthesis of compounds of formula (I):

Example of Method AA:

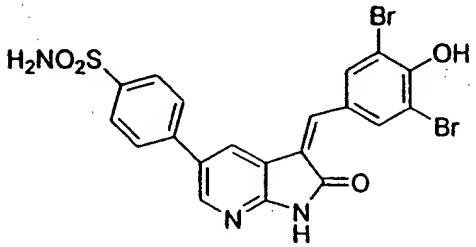


Example 20: 5-Bromo-3-[1-(3,5-dichlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

The following reagents were combined under N_2 at room temperature: 5-Bromo-7-aza-oxindole (0.020 g, 0.93 mmol), 1-(3,5-dichlorophenyl)-pyrrole-2-carboxaldehyde (0.0225 g, 0.93 mmol), toluene (1 mL), and 4-methylmorpholine (1 drop). The reaction temperature was increased to 110 °C for 6 hours. A solid had precipitated from the reaction mixture. The reaction was cooled to room temperature and the solid was collected by filtration, washed with toluene (3 mL)

and Et_2O (5 mL). The solid was dried in vacuo to afford the title compound as a yellow solid. (0.026 g, 64% yield). ^1H NMR (d^6 DMSO) δ 6.60 (m, 1H); 7.20 (s, 1H); 7.26 (s, 1H); 7.60 (m, 3H); 7.75 (s, 1H); 8.21 (d, 2H); 11.31 (bs, 1H). Electrospray MS: 434, 436, 438 (MH+).

Example of Method BB:



Example 9: 4-[3-(3,5-Dibromo-4-hydroxy-benzylidine)-2-Oxo-2,3-dihydro-1H-pyrrolo [2,3-b] pyridin-5-yl] benzenesulfonamide.

A mixture of 0.075 g (0.26 mmol) of 5-(4-benzene sulfonamide)-7-aza-oxindole and 0.087 g (0.31 mmol) of 3,5-dibromo-4-hydroxybenzaldehyde was stirred in 1 ml of HOAc. 50 ml of concentrated HCl was added and the mixture was heated to 80°C for 42 hrs. After cooling to ambient temperature the reaction mixture was diluted with EtOAc. The solid was collected by vacuum filtration and washed with EtOAc and Et_2O to yield 4-[3-(3, 5-Dibromo-4-hydroxy-benzylidine)-2-Oxo-2, 3-dihydro-1H-pyrrolo [2, 3-b] pyridin-5-yl] benzenesulfonamide as a yellow solid (0.103 g, 72%): ^1H NMR (DMSO-d_6): δ 7.39 (s, 2H), 7.89 (s, 4H), 7.94 (s, 1H), 8.39 (d, J = 2 Hz, 1H), 8.48 (d, J = 2 Hz, 1H), 8.75 (s, 2H), 11.45 (s, 1H); ESI-MS: *m/z* 550 $(m-H)^-$.

The following Examples were obtained using the above described reaction schemes, routes and synthesis strategies, but with the appropriate reagent, reaction conditions and reactant substitutions that will be readily realized by those of ordinary skill in this art, without the exercise of undue experimentation.

Example 1: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO): 11.46 (s, 1H), 8.81 (s, 2H), 8.44 (s, 1H), 8.32 (s, 1H), 7.99 (s, 1H), 7.60 (d, 1H, J = 5.1 Hz), 7.54 (d, 1H, J = 3.0 Hz), 7.20 (dd, 1H, J = 3.0, 5.1 Hz).

MS (-ve APCI): 480 (12, M+2), 479 (55, M+1), 478 (20, M^+), 477 (100).

Example 2: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO): 11.42 (s, 1H), 8.80 (s, 2H), 8.44 (s, 1H), 8.37 (s, 1H), 7.99 (s, 1H), 7.73 (d, 2H, J = 7.3 Hz), 7.52 (t, 2H, J = 7.3 Hz), 7.41 (t, 1H, J = 7.3 Hz).

MS (-ve ES): 470 (10, M^+), 471 (45, M-H).

Example 3: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-vunyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO): 11.36 (s, 1H), 8.76 (s, 2H), 8.26 (s, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 6.77 (dd, 1H, J = 10.6, 17.8), 5.87 (d, 1H, J = 17.8 Hz), 5.30 (d, 1H, J = 10.6 Hz).

MS (-ve ES): 423 (22, M+1), 422 (10, M^+), 421 (60), 198 (40), 163 (95), 162 (100).

Example 4: 5-Acetyl-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO): 11.77 (s, 1H), 8.81 (s, 2H), 8.79 (s, 1H), 8.52 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 2.62 (s, 3H).

MS (-ve ES): 439 (22, M+1), 438 (8, M^+), 437 (38), 279 (100).

Example 7: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO): 11.46 (s, 1H), 8.82 (s, 1H), 8.78 (s, 2H), 8.45 (s, 1H), 8.27 (s, 1H), 7.92 (s, 1H), 7.59 (m, 1H), 6.93 (d, 1H, J = 3.3 Hz), 6.40 (d, 1H, J = 3.3 Hz).

MS (-ve ES): 463 (28, M+1), 462 (26, M^+), 461 (100, M-H), 459 (55).

Example 8: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-3-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 7.57 (d, 1H, J=5.2 Hz); 7.68 (m, 1H); 7.84 (s, 1H); 7.87 (s, 1H); 8.35 (s, 1H); 8.47 (s, 1H); 8.73 (s, 2H); 11.35 (s, 1H).

Electrospray MS (ES+) 476.6, 478.7, 480.7; (ES-) 474.8, 476.7, 478.7.

Example 9: 4-[3-(3, 5-Dibromo-4-hydroxy-benzylidine)-2-Oxo-2,3-dihydro-1H-pyrrolo [2, 3-b] pyridin-5-yl] benzenesulfonamide.

A mixture of 0.075 g (0.26 mmol) of 5-(4-benzene sulfonamide)-7-aza-oxindole and 0.087 g (0.31 mmol) of 3,5-dibromo-4-hydroxybenzaldehyde was stirred in 1 ml of HOAc. 50 ml of concentrated HCl was added and the mixture was heated to 80°C for 42 hrs. After cooling to ambient temperature the reaction mixture was diluted with EtOAc. The solid was collected by vacuum filtration and washed with EtOAc and Et_2O to yield 4-[3-(3, 5-Dibromo-4-hydroxy-benzylidine)-2-Oxo-2, 3-dihydro-1H-pyrrolo [2, 3-b] pyridin-5-yl] benzenesulfonamide as a yellow solid (0.103 g, 72%): ^{1}H NMR (DMSO-d_6): δ 7.39 (s, 2H), 7.89 (s, 4H), 7.94 (s, 1H),

8.39 (d, J = 2 Hz, 1H), 8.48 (d, J = 2 Hz, 1H), 8.75 (s, 2H), 11.45 (s, 1H); ESI-MS: *m/z* 550 (m-H)$^-$.

Example 12: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid benzyl ester

^{1}H NMR (d^6 DMSO): 11.80 (s, 1H), 8.84 (s, 2H), 8.76 (d, 1H, *J* = 1.8 Hz), 8.53 (d, 1H, *J* = 1.8 Hz), 8.07 (s, 1H), 7.36-7.54 (m, 6H), 5.42(s, 2H).

MS (-ve APCI): 530 (4, M$^+$), 396 (24), 394 (100).

Example 13: Isopropyl-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-2-oxo-1,2-dihydro-3*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate

^{1}H NMR (d^6 DMSO): 11.74 (s, 1H), 8.71 (s, 1H), 8.33 (s, 1H), 8.03 (s, 2H), 7.75 (s, 1H), 5.14 (m, 1H, *J* = 6.2 Hz), 1.32 (d, 6H, *J* = 6.2 Hz).

MS (-ve APCI): 482 (5, M$^+$), 441 (35), 439 (100), 397 (52), 395 (80).

Example 16: 5-(2-Amino-thiazol-4-yl)-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO): 11.44 (s, 1H), 8.73 (s, 2H), 8.47 (s, 1H), 8.34 (s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.83 (s, 1H), 7.23 (s, 1H) 7.01 (s, 1H).

MS (-ve APCI): 495 (5, M+1), 415 (16), 198 (25), 165 (50), 163 (100).

Example 20: 5-Bromo-3-[1-(3,5-dichlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

The following reagents were combined under N_2 at room temperature: 5-Bromo-7-aza-oxindole (0.020 g, 0.93 mmol), 1-(3,5-dichlorophenyl)-pyrrole-2-

carboxaldehyde (0.0225 g, 0.93 mmol), toluene (1 mL), and 4-methylmorpholine (1 drop). The reaction temperature was increased to 110 °C for 6 hours. A solid had precipitated from the reaction mixture. The reaction was cooled to room temperature and the solid was collected by filtration, washed with toluene (3 mL) and Et_2O (5 mL). The solid was dried in vacuo to afford the title compound as a yellow solid. (0.026 g, 64% yield). ^{1}H NMR (d^6 DMSO) δ 6.60 (m, 1H); 7.20 (s, 1H); 7.26 (s, 1H); 7.60 (m, 3H); 7.75 (s, 1H); 8.21 (d, 2H); 11.31 (bs, 1H).
Electrospray MS: 434, 436, 438 (MH+).

Example 22: 3-(3,5-Dibromo-4-hydroxybenzylidene)-5-ethyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO): 11.26 (s, 1H), 8.78 (s, 2H), 7.98 (s, 1H), 7.92 (s, 1H), 7.82 (s, 1H), 2.62 (q, 2H, J = 7.6 Hz), 1.24 (t, 3H, J = 7.6 Hz).

MS (-ve APCI): 161 (100, M-H).
MS (+ve APCI): 425 (18, M+1), 423 (16), 141 (61), 109 (100).

Example 25: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester

^{1}H NMR (d^6 DMSO): 11.67 (s, 1H), 8.66 (s, 1H), 8.30 (s, 1H), 7.97 (s, 2H), 7.69 (s, 1H), 4.24 (q, 2H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz).

MS (-ve APCI): 468 (8, M^+), 439 (20), 394 (8), 326 (58), 288 (100).

Example 27: 3-(3-Bromo-4-hydroxy-5-(2'-methoxyphenyl)-benzylidene)-5-bromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3H); 7.04 (m, 1H); 7.17 (d, 1H, J=8.40 Hz); 7.24 (m, 1H); 7.45 (d, 1H, J=7.5 Hz); 7.95 (s, 1H); 8.11 (d, 1H, J=2.1 Hz); 8.19 (d, 1H, J=2.1 Hz); 8.25 (d, 1H, J=1.8 Hz); 8.96 (d, 1H, J=2.1 Hz); 11.42 (bs, 1H).

APCI MS: 499 (60%), 501 (100%), 503 (60%), (M-H).

Example 28: 5-Bromo-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (d^6 DMSO) δ 11.47 (s, 1H), 8.73 (s, 2H), 8.21 (s, 1H), 8.19 (s, 1H), 7.8 (s, 1H).

MS (AP-ve) 475 (100) (M-H).

Example 29: 5-Bromo-3-[(3-phenoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 7.04 (d, 2H, J=6.30 Hz); 7.15 (m, 2H); 7.39 (m, 2H); 7.50 (dd, 1H, J=6.0 Hz); 7.97 (s, 1H); 8.02 (d, 1H, J=5.70 Hz); 8.16 (m, 2H); 8.29 (d, 1H, J=1.50 Hz)); 11.41 (bs, 1H).

Electrospray MS (ES+) 393.3, 395.2

Example 30: 6-chloro-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1*H*-pyrrolo[2,3-*b*]pyridin-2-one

^{1}H NMR (DMSO-*d6*) (E-isomer): δ 7.09 (d, 1H, J = 8.0 Hz), 7.68 (s, 1 H), 7.78 (d, 1H, J = 8.0 Hz), 7.95 (s, 2H), 11.51 (s, 1H). (Z-isomer): δ 7.17 (d, 1H, J = 8.0 Hz), 7.85 (s, 1 H), 8.00 (d, 1H, J = 7.9 Hz), 8.77 (s, 2H), 11.55 (s, 1H).

MS (+ve AP) 429 (45%), 431 (100), 433 (68%), 435 (10%) (M+H).

Anal. Calcd. for $C_{14}H_7Br_2ClN_2O_2$: C, 39.18; H, 2.26; N, 5.71; Br, 32.58; Cl, 7.23. Found: C, 38.89; H, 2.16; N, 5.85; Br, 32.46; Cl, 7.20.

Example 35: 5-bromo-3-[(*Z*)-(3,5-dimethyl-1*H*-pyrrol-2-yl)methylidene]-1*H*-pyrrolo[2,3-*b*]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3H); 2.37 (s, 3H); 6.11 (s, 1H); 7.80 (s, 1H); 8.08 (d, 1H, J=1.5 Hz); 8.41 (d, 1H, J=1.5 Hz); 10.65 (bs, 1H); 13.23 (bs, 1H).

APCI MS 319 (MH+)

Example 37: 3-[2-Furylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 6.88 (s, 1H); 7.40 (d, 1H, J=3.6 Hz); 7.54 (s, 1H); 7.64 (d, 1H, J=5.1 Hz) 7.72 (m, 1H); 7.96 (s, 1H); 8.37 (s, 1H); 8.54 (s, 1H); 8.84 (s, 1H); 11.29 (s, 1H).

Electrospray MS (ES+) 295.2 (MH+)

Example 38: 3-(-4-[3-(dimethylamino)propoxy]phenylmethylidene)-5-(3-thienyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H); 2.18 (s, 6H); 2.40 (m, 2H); 4.14 (m, 2H); 7.17 (d, 2H, J=8.7 Hz); 7.48 (d, 1H, J= 4.8 Hz); 7.69 (m, 1H); 7.79 (s, 2H); 7.83 (d, 2H, J=8.7 Hz); 8.19 (s, 1H); 8.50 (s, 1H); 11.30 (s, 1H),

Electrospray MS (ES+) 405 (MH+)

Example 41: 5-Bromo-3-[(4-hydroxy-3,5-diisopropylphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 1.22 (d, 12H); 3.42 (m, 2H); 7.43 (s, 2H); 7.80 (s, 1H); 8.06 (s, 1H); 8.24 (s, 1H); 9.11 (bs, 1H); 11.40 (bs, 1H).

Electrospray MS: 401 (70%); 403 (100%).

Example 42: 3-[(4-Hydroxy-2-methoxyphenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H); 6.51 (m, 2H); 7.32 (m, 1H); 7.42 (m, 2H); 7.53 (d, 2H, J=7.2 Hz); 7.68 (d, 1H, J= 8.0 Hz); 7.80 (s, 1H); 7.98 (s, 1H); 8.32 (s, 1H); 11.20 (s, 1H).

MS AP+ 344 (M+1); AP+ 328 (M-16+1); AP- 326 (M-16+1)

Example 45: 3-[(3,5-Dichloro-4-hydroxyphenyl)methylidene]-5-(2-furyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6) δ 6.17 (m, 1H); 6.84 (d, 1H, J=3.30 Hz); 7.70 (s, 1H); 7.76 (s, 1H); 7.88 (s, 2H); 8.13 (d, 1H, J=1.50 Hz); 8.53 (d, 1H, J=1.80Hz); 11.41 (bs, 1H).

Electrospray MS (ES-) 371 (M-H)

Example 46: 3-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylidene]-5-(2-furyl)-1H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6): δ 2.32 (s, 6H), 6.04 (s, 1H), 6.59 (m, 1H), 6.89 (d, J = 3 Hz, 1H), 7.73 (s, 1H), 7.75 (s, 1H), 8.33 (s, 1H), 8.37 (s, 1H), 11.44 (s, 1H), 13.23 (s, 1H)

ESI-MS: *m/z* 306 $(m+H)^+$.

Example 47: 5-(2-Furyl)-3-[(4-hydroxy-2-methoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H), 6.54 (m, 3H), 6.78 (d, J = 3 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.70 (s, 1H), 7.79 (s, 1H), 8.00 (s, 1H), 8.43 (d,J = 1.6 Hz, 1H), 10.34 (bs, 1H), 11.23 (s, 1H)

ESI-MS: *m/z* 335 $(m+H)^+$.

UTILITY

Kinase signal transduction results in, among other responses, cell proliferation, differentiation and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma; psoriasis, arteriosclerosis, arthritis and diabetic retinopathy or other disorders related to uncontrolled angiogenesis and/or vasculogenesis.

The efficacy of compounds of the present invention as inhibitors of protein kinase activity can be evaluated and measured using pharmacological methods known in the art or as described in detail below based on similarly established methodologies.

Substrate phosphorylation assay examples:

A. cRaf1 Assay

Human cRaf1 tagged with poly histidine at the carboxyterminus was expressed in a baculovirus expression system and purfied by Ni chelate affinity chromatography. Human MEK1 was expressed in *e. coli* as a fusion protein with Glutathione-S-transferase, and purified by glutathione sepharose affinity chromatography. Typically assays were performed in a final volume of 40 - 100 mL with and without inhibitors. Reactions contained cRaf1 (20 nM), MEK1 (100-500 nM), [γ-^{32}P]ATP (10-20 mM), Mg^{2+} (10 mM), MOPS (50 mM, pH 7.5). Reactions were incubated at room temperature for periods of time ranging from 20-120 minutes. Inhibitors were diluted in 100% DMSO prior to addition to the

assay. Reactions were terminated with an equal volume of 0.5% phosphoric acid. MEK1 phosphorylation was detected by scintillation counting following collection of protein onto phosphocellulose filters.

B. Raf/MEK Cascade Assay

Human cRaf1 and MEK1 were purified as described above. A peptide substrate phosphorylated by MEK1 was used as the final phosphoryl group acceptor. The sequence of the peptide HTGFLTEYVATRWKK-OH was derived from the site in ERK2 that is phosphorylated by MEK1. Assay conditions were the same as those described above except for the following modifications. Reactions contained cRaf1 (1-5 nM), MEK1 (60 nM), and peptide (250 mM).

C. CDK1 and CDK2 Assay

Cyclin dependent protein kinase assays utilized the peptides Biotin-aminohexyl-AAKAKKTPKKAKK and Biotin-aminohexyl-ARRPMSPKKKA-NH_2 as phosphoryl group acceptors. CDK1 and CDK2 were both expressed utilizing a baculovirus expression system and were partially purified to comprise 20-80% of total protein, with no detectable competing reactions present. Typically, assays were performed by incubating either enzyme (0.2-10nM), with and without inhibitor, one of the two peptide substrates (1-10nM), [γ-^{32}P]ATP (1-20nM), and 10-20mM Mg^{2+} for periods of time generally within the range 10-120 minutes. Reactions were terminated with 0.2-2 volumes of either 20% acetic acid or 50-100mM EDTA buffered to pH 7 (substrate consumption < 20%). The buffer employed in enzyme assays was either 30mM HEPES 7.4 containing 0.15M NaCl and 5% DMSO, the buffer 50mM MOPS 7.0 containing 0.15M NaCl and 5% DMSO, or the buffer 100mM HEPES pH 7.5 containing 0.1mg/mL BSA and 5% DMSO. Inhibitors were diluted in 100% DMSO prior to addition into the assay. Detection of peptide phosphorylation was accomplished by scintillation counting following either collection of peptide onto phosphocellulose filters (for reactions stopped with acetic acid), collection of peptide in wells of 96 well plates coated with Streptavidin (Pierce) (reactions were stopped with EDTA), or addition of Avidin coated Scintillant impregnated beads (Scintillation Proximity Assays from

Amersham, reactions were stopped with EDTA). Counts detected by any of these methodologies minus the appropriate background (assays with additional 40mM EDTA or lacking peptide substrate) were assumed to be proportional to the reaction initial rates, and IC50s were determined by a least squares fit to the equation CPM = V_{max}*(1-([I]/(K+[I])))+nsb, or -pIC50s were determined by a fit to the equation CPM = nsb+(V_{max}-nsb)/(1+(x/10^x-pIC50)), where nsb are the background counts.

D. UL97

UL97 was produced as a GST fusion protein from a baculovirus vector expressed in sf9 cells as described by He (He et al., 1997). UL97 was assayed as a protein kinase using ^{32}P transfer from ATP to histone H2B with detection of radiolabeled histone bound to phosphocellulose. Assay mixes for testing inhibitors of UL97 activity contained 2 mM [$\gamma^{32}P$]-ATP, 15 mM histone H2B, 50 mM sodiumCHES, pH 9.5, 1 M NaCl, 2 mM dithiothreitol and 10 mM $MgCl_2$. Inhibitors were dissolved in diluted DMSO to give a final DMSO concentration in the reaction of 1% DMSO. After incubation at 20°C, the reactions were terminated by addition of 10 volumes of 75 mM phosphoric acid, 30 mM ATP, 1 mM EDTA, then were spotted onto phosphocellulose filters and washed four times with 75 mM phosphoric acid. Radioactivity was determined by liquid scintillation counting.

E. SRC/lck Enzyme Assay

The peptide substrates used in Src and Lck assays were biotin-aminohexyl-EEIYGEF-NH_2 (Src) and biotin-aminohexyl-EAIYGVLFAKKK-NH_2 (Lck). The src and lck proteins were purified to homogeneity from a baculovirus expression system and preactivated before adding to assay mixtures. The maximum activation was achieved by incubating concentrated enzyme (10-30 mM) on ice for 40 min in the presence of 1 mM ATP and 10 mM $MgCl_2$ in 100 mM HEPES, pH 7.5. The activated enzyme was diluted to 2 nM into an 50 mL reaction mixture containing 100 mM HEPES, pH 7.5, 5 mM ATP, 10 mM $MgCl_2$, 2 mM peptide, 0.05 mg/mL BSA, and an inhibitor at varying concentrations and with or without 8 mCi/mL [γ-^{33}P]ATP dependent upon the method of analysis for the extent of

reaction. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were allowed to proceed for 30 min at room temperature and quenched with addition of EDTA to 50 mM in 220 mL. The extent of reactions was analyzed in one of the two ways: an Elisa-based and a radioactive isotope-based. The quenched samples (200 mL) were transferred to a neutravidin coated plate (Perice) and incubated at room temperature for 40 min to allow biotinylated peptide to bind to neutravidin. The unbound peptide and the rest of the solution was washed away using a plate washer. In the Elisa format, a 200 mL HRP-PY20 anti phosphotyrosine antibody conjugate solution was added. After incubation for about 30 min, the plated was washed to remove unbound antibody-HRP conjugate. An Elisa substrate, K-blue (Neogen), was added and the Elisa reaction quenched with Red-stop (Neogen) after 15 min. The plate was read at A_{625} in a plate reader. In the isotope-based format, the reactions had been performed in the presence of [γ-^{33}P]ATP. 200 mL Scintiverce DB was added to each well of the plate with bound biotin-peptide. The plate was sealed and counted in a micro-b-counter (Wallac). IC_{50} values were obtained by fitting raw data to A_{625} (cpm) = V_{max}*(1-([I]/(IC_{50}+[I])))+ b, where b is background.

F. VEGFR-2 Tyrosine Kinase Assay

The peptide substrate used in the VEGFR-2 assay was biotin-aminohexyl-EEEEYFELVAKKKK-NH_2. The kinase domain of the enzyme was purified to homogeneity from a baculovirus expression system. The enzyme was preactivated on ice for 15 min in the presence of 100 µM ATP and 20 mM $MgCl_2$, and stored at -80°C until needed for assay. The activated enzyme was diluted to 0.4 nM into a 60 µl reaction containing 100 mM HEPES, pH 7.5, 5 µM ATP, 10 mM $MgCl_2$, 5 µM peptide, 0.1 mM DTT, 0.05 mg/ml BSA, and an inhibitor at varying concentrations. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were incubated for 30 min at room temperature, and then quenched by the addition of EDTA to 60 mM in 210 µl. The quenched samples (190 µl) were transferred to a neutravidin-coated plate (Pierce) and incubated at room temperature for 40 min to

allow biotinylated peptide to bind to the neutravidin. The unbound components of the reaction were removed by washing with a plate washer, then 200 µl HRP-PY20 anti-phosphotyrosine antibody conjugate was added to each well. After incubation for 40 minutes, the plate was washed to remove any unbound anitbody. A HRP substrate, K-blue (Neogen) was added and the reaction was quenched with Red Stop (Neogen) after 20 min. The absorbance of the wells was read at A_{650} in a plate reader. IC_{50} values were obtained by fitting raw data to $A_{650} = V_{MAX} * (1-[I]/IC_{50} + [I]))) + b$, where b is background.

G. Tie-2 Kinase Assay

Reaction: 0.5 µM 3T68, 75 µM ATP, 50 mM $MgCl_2$, 0.1 M Hepes, 0.1 mM DTT, 10 nM Tie-2. Enzyme reaction: 30 minutes at room temperature. Stop reaction with 100 uL 0.15 M EDTA. Transfer 125 uL to Neutravidin plate, incubate 30 minutes at room temperature. Wash plate with 300 uL H_2O, 5 times. Add 150 uL Eu-anti-pY (1:2000, kept at 4 °C) and incubate for 30 minutes at room temperature. Wash plate with 300 uL H_2O, 5 times. Add 150 uL enhancement solution. Enzyme stability: stable for 24 hours at 250 nM in 6.25 mM DTT, 0.1 M Hepes, 0.1 mg/mL BSA, 4 °C.

H. c-fms Assay

It is necessary to "preactivate" the enzyme to increase its' activity for the purpose of producing a good enzyme activity (signal) for the screening of compounds. C-fms is preactivated using the following conditions: 1mg/ml c-fms, 500µM ATP, 20mM $MgCl_2$, 50mM MOPS, pH 7.62 hour, room temperature incubation. Following the designated incubation time (2 hours), the enzyme is diluted to 75nM (~1:250) with room temperature 50mM MOPS, pH 7.6 and used in the Enzyme Assay described as follows. Substrate Solution (for screening): 50mM MOPS, pH 7.6, 25µM ATP, 20mM $MgCl_2$, 25µM EGFR peptide (EEEEYFELVAKKK). Enzyme assay (for screening): Enzyme assays are performed in round-bottom polystyrene 96-well plates. 45ul assay volume/well which includes 15ul of preactivated (diluted 1:250) c-fms enzyme solution, 15ul of substrate solution and 15ul of 6% DMSO (controls) or compound in 6%

DMSO. The final concentration of DMSO in the assay is 2%. Control wells, generally in A12-D12, include the addition of 15ul of 6% DMSO. Background wells, generally in E12-H12, include the addition of 15ul of 0.5M EDTA. Compounds in 6% DMSO are added to the round-bottomed 96-well plates. Enzyme solution and substrate solution are added using a Beckman Biomek 2000. The kinase (enzyme) assay is performed at room temperature for 30'. The reactions are stopped by the addition of 45ul 0.5% phosphoric acid, 60ul of this mix is transfered to 96-well MAPH (phosphocellulose) filter plates. The filter plates are placed on a vacuumn manifold, filtered, and washed 3 times with 0.5% phosphoric acid. After washing, the plate bottoms are blotted on a paper towel, the bottom plastic (seal) piece is removed and the plate is placed in a Packard multiscreen adapter. 30ul of Optiphase supermix scintillation fluid is added to each well. The plates are sealed using a Packard plate sealer, placed in a Packard 96-well plate topcount scintillation counter for CPM determination. Data reduction is performed using the Microsoft Addin Robosage using the curve fitting function , y=(Vmax*x)(k+x). and data reduction formula 100*(U1-C2)/(C1-C2).

I. p38 kinase assay

The peptide substrate used in the p38 assay was biotin-IPTSPITTTYFFFRRR-amide. The p38 and MEK6 proteins were purified to homogeneity from E.coli expression systems. The fusion proteins were tagged at the N-terminus with Glutathione-S-Transferase (GST). The maximum activation was achieved by incubating 20uL of a reaction mixture of 30nM MEK6 protein and 120nM p38 protein in the presence of 1.5μM peptide and 10mM $Mg(CH_3CO_2)_2$ in 100mM HEPES, pH 7.5, added to 15uL of a mixture of 1.5μM ATP with 0.08uCi [g-^{33}P]ATP, with or without 15uL of inhibitor in 6%DMSO. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were allowed to proceed for 60 min. at room temperature and quenched with addition of 50uL of 250mM EDTA and mixed with 150uL of Streptavidin SPA beads (Amersham) to 0.5mg/reaction. The Dynatech Microfluor white U-bottom plates were sealed and the beads were allowed to settle

overnight. The plates were counted in a Packard TopCount for 60 seconds. IC_{50} values were obtained by fitting raw data to %I = 100*(1-(I-C2)/(C1-C2)), where I was CPM of background, C1 was positive control, and C2 was negative control.

The results shown in the following Tables (3-9) summarize representative data. The key listed below can be used for Tables 3 through 9.

Key	symbol	range
	+	IC_{50} < 1 μM
	++	IC_{50} from 1- 10 μM
	+++	IC_{50} from 10- 100 μM

Table 3 illustrates the inhibitory activity of representative compounds of the present invention against raf kinase.

Table 3

Example	Raf
28	+
6	+
5	+
8	+
7	+
1	+
2	+
4	+
10	+
11	+
14	+

15	+
22	+
25	+
24	+
13	+
31	+
34	++
26	+
44	+
45	+

Table 4 illustrates the inhibitory activity of representative compounds of the present invention against TIE2 kinase.

Table 4

Example	Tie 2
7	+
2	++
33	++
41	+
55	++
52	+

Table 5 illustrates the inhibitory activity of representative compounds of the present invention against CDK2.

Table 5

Example	CDK2
28	+
5	+
3	+
22	+
36	+

Table 6 illustrates the inhibitory activity of representative compounds of the present invention against VEGFR Tyrosine Kinase.

Table 6

Example	VEGFR
28	++
3	+
4	++
21	++
14	+
20	++
15	+
16	+
27	++
32	++
35	+
36	+
37	+
38	+
39	+

43	+
48	++
53	++
49	+
54	+
55	+
52	+

Table 7 illustrates the inhibitory activity of representative compounds of the present invention against c-fms kinase.

Table 7

Example	c-fms
6	+
8	+
1	+
2	+
10	+
21	++
18	++
16	+
35	+
37	+
38	+
39	++
40	++
42	+
43	++
46	+
48	+

49	+
50	++
48	+
53	++
49	+
54	++
51	++
55	++
50	+
52	++

Table 8 illustrates the inhibitory activity of representative compounds of the present invention against p38 kinase.

Table 8

Example	P 38
28	+
11	++
27	+
22	+
30	+

Table 9 illustrates the inhibitory activity of representative compounds of the present invention against raf kinase.

Table 9

Example	Src
23	+

3	+
11	++
9	+
24	++

Cell-based assay examples:

As may be expected in light of specific inhibitory activity of these compounds against several kinases involved in growth regulation, angiogenesis, and inflammation, the compounds of this invention have properties which can be directly demonstrated in several cell-based assays. Representative assays are described below and representative data is summarized in Table 10.

A. MTT assay

The potency of compounds of the invention are tested for their ability to inhibit cell proliferation and cell viability. The metabolic conversion of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma #M2128) to a reduced form is a commonly used measure of cellular viability. Following is the procedure:

Cells are maintained in 75cm^2 tissue culture flasks until ready for use. The cells are grown and plated for the assay in Dulbecco's modified Eagle's media containing 10% fetal bovine serum. For example, the following cell lines can be used: a) human foreskin fibroblasts (HFF), b) HT29 (human colon carcinoma cell line), c) MDA-MB-468 (human breast carcinoma cell line), d) RKO (human colon adenocarcinoma cell line), e) SW620 (human colon carcinoma cell line), f) A549 (human lung carcinoma cell line), and g) MIA PACA (human pancreatic carcinoma cell line). Cells are maintained at 37^o C in 10% CO_2, 90% humidified air. Cells are plated in 96-well tissue culture plates at the densities listed below. 100µL of cell suspension is added to each well of the 96-well plate except the top row of the plate which contains no cells and serves as a reference for the spectrophotometer.

Cell line	Density
HFF	2500cells/well
HT29 cell lines	2500 cells/well
MDA-MB-468 cell line	5000 cells/well
SW620	4000 cells/well
MIA PACA	3000 cells/well
PC-3	4500 cells/well

Cells are incubated overnight in Dulbecco's modified Eagle's media containing 10% fetal bovine serum at 37° C in 10% CO_2, 90% humidified air prior to dosing. Cells are dosed in 10 sequential 3-fold dilutions starting at 30μM depending upon the solubility of the compound. Compounds with solubilities of less than 30μM are dosed at the highest soluble concentration. Stock solutions of compounds are made in 100% dimethyl sulfoxide (DMSO). Stock solutions are diluted in Dulbecco's modified Eagle's media containing 100μg/mL gentamicin and 0.3 to 0.6% DMSO at the twice the highest concentration to be placed on the cells. If compounds have been dissolved in DMSO the final concentration of DMSO on the cells is kept below 0.3%. 3-fold serial dilutions are performed on each compound to prepare 10 concentrations of the compound for dosing. 100μL of diluted compound is added to the 100μL of media currently on the dish. For each concentration of compound, 2-4 replicate wells are prepared.

Cells are returned to incubator and allowed to proliferate in the presence of compound for 72 hours before addition of MTT. MTT is prepared in phosphate buffered saline (Irvine Scientific #9240) at a concentration of 2mg/mL. 50μL per well of MTT solution is added to the 200μL of media to yield a final concentration of 0.4mg/mL and plates are returned to the incubator for 4 hours. After 4 hours incubation the media, compound and MTT mixture is aspirated from the plates and 100 μL of 100% DMSO is added to each well in addition to 25μL of Sorenson's Buffer (0.1M glycine, 0.1M NaCl, pH 10.5). Quantitation of metabolic reduction of MTT in each plate is performed by reading optical density at 570nm

wavelength on a Molecular Devices UVmax microplate reader. Growth inhibition curves and 50% inhibitory concentrations are determined using Microsoft Excel.

B. HUVEC MTT Assay Protocol

The following protocol may also be used to measure a compound's activity.

Cell culture: HUVEC (human umbilical vein endothelial cells) from Clonetics, cat. # CC-2519 (cryopreserved cells pooled from several donors). EGM-MV BulletKit, Clonetics cat. # CC-3125. Trypsin/EDTA, Clonetics cat. # CC-5012. Fibronectin cellware from Becton Dickinson: 96-well plates, cat. # 40409. T-75 flasks, cat. # 40521. T-150 flasks, cat. # 40526 Plate HUVECs in complete Clonetics medium at 3500 cells/well in 96-well coated plates. (This is the number plated for up to a 3-day assay.) Place 100 µl per well in the first 11 columns of the 96-well plate starting at the left side. Put 100 µl of medium in the last column on the right of each plate. Grow in 5% CO_2 incubator overnight.

Compound dosing: Compound stocks are made in DMSO at 10 mM. To prepare a 60 µM starting solution, add 6 µl of the 10 mM stock solution to 1 ml of medium. Prepare 1:3 serial dilutions in medium containing 0.6% DMSO for a total of 10 compound concentrations. We use deep well plates for this and do the dilutions with a Biohit 8-channel electronic pipetter. We typically do each compound dilution series in duplicate. Place 100 µl of each dilution in the appropriate well on the cell culture plate. (After 100 µl of compound solution is added to 100 µl of cells, the highest final concentration on the plate will be 30 µM.). Alternatively, one can plate the cells in complete medium but then prepare 1X stocks (30 µM and lower) of the compounds in the Clonetics medium containing only the supplied FBS, antibiotics, and hydrocortisone, plus 5 ng/ml VEGF. In this procedure the complete medium is aspirated from the cell culture plates and 200 µl of each compound solution is added per well.

MTT detection: After selected time of exposure, add 50 µl of MTT stock (2 mg/ml in PBS) and return to incubator. Plate multiple HUVEC plates for each compound

plate and then reading one set of plates each after 24, 48, and 72 hr. After 4 hr incubation, aspirate the medium and MTT. Add 100 µl DMSO to each well and follow with 25 µl Sorenson's buffer (0.1 M glycine, 0.1 M NaCl, pH 10.5). Read at 570 nm with automix on Molecular Devices Uvmax plate reader.

C. Cell-Based TNFa Release Inhibition Protocol

The potency of the compounds of the invention as inhibitors or relese of soluble tumor necrosis factor a from stimulated monocytes in vitro is determined as follows; LPS/PMA solution for assay consisting of a) 4 µL of 5 mg/mL LPS stock and b) 6 µL of 10 mg/mL PMA stock are added to 500 µL of medium (RPMI 1640 (Gibco) + 10% FBS + penicillin/streptomycin + 1-glutamine). This solution is then 1:1000 (40 ng/mL and 120 ng/mL) for use later in the assay. Compounds (10 mM) are serially diluted 1:3 in DMSO. Compound dilutions (20 µL) are added to a sterile round bottom 96 well plate (20 µL:200 µL total volume = 1:10 for final concentrations of 50 µM for test compounds). MonoMac 6 cell suspension (130 µL, 1.5 x 10^6 cells/mL) is then added to each well resulting in 2 x 10^5 cells/well. LPS/PMA (50 µL) solution is then added to each well to begin stimulation (final concentrations of 10 ng/mL and 30 ng/mL respectively). The plate is incubated as 37 °C for 2 hours then spun at 1500 rpm for 3 minutes to pellet cells. The supernatant (120 µL/well) is removed to a new round bottom 96 well plate and diluted 1:10 in PBS. Then, 20 µL of the supernatant is transferred to a Cistron TNFa ELIZA plate and processed according to the manufacturer's instruction to quantitate levels of TNFa. Percent inhibition of TNFa release is calculated at each inhibitor concentration and the data were plotted using standard curve fitting programs. IC_{50} values were determined from these curves.

Representative cell-based data are summarized in Table 10. Table 10 illustrates the inhibitory activity of compounds of the present invention in the HUVEC cell based assay and the TNFa release assay. Data for the cytotoxicity of representative compounds of the present invention are also shown for representative human tumor cell lines.

Table 10

Example #	MTT HT-29 (colon)	MTT MDA468 (breast)	HUVEC
1	++	++	ND
2	++	++	++
3	++	++	++
7	++	++	++
8	++	++	++
12	++	++	ND
13	++	++	ND
22	++	++	ND
24	++	++	ND
25	++	++	ND

Key	symbol	range
	+	IC_{50} < 1 μM
	++	IC_{50} from 1- 50 μM
	+++	IC_{50} from 50- 100 μM
	ND	No data

IN VIVO ASSAYS

The following *in vivo* assay may be conducted to measure the effect of the claimed compounds upon *in vivo* tumor growth as a result of the compound's interaction with protein kinases. Unless otherwise specified, the following assays may be generally applied to measure the activity of a compound against many different tumor xenografts. To the extent that an assay, set forth below, refers to a specific tumor cell line, one skilled in the art would be able to adapt the disclosed protocol for use to measure the activity of the compounds in alternate tumor cell lines.

Anti-Tumor Studies: Animals

Mice are acquired from Taconic Farms and are maintained in Microisolator cages at 72 ± 2°F with a 12 hour light/dark cycle. Animals are housed at 4 mice per cage (28 x 17 x 12 cm) and are given food and water ad libitum. Animals are numbered through the use of an ear punch or tail tattoo. All animal handling is done in a laminar flow hood.

Tumor implantation

The tumor cell lines used for the protein kinase project are the colon lines SW620, RKO, HT-29. Tumors are initiated by subcutaneous injection of a cell suspension into the right flank of each mouse. The inoculum consists of 2×10^6 cells/mouse/ 0.2 ml in PBS:matrigel (1:1).

Cell growth

SW620, available from the American Type Culture Collection, are grown in media consisting of RPMI 1640 with fetal bovine serum (10%), sodium pyruvate (1.0 mM) and glutamine (2.0 mM). Cells are incubated at 37°C in 5% CO_2. Cells are harvested with trypsin (0.05%), centrifuged, and resuspended in PBS:matrigel (1:1) at 1×10^7 cell/ml.

Tumor measurement

Solid tumors are measured by caliper measurement through the skin. Caliper measurements are typically made twice weekly. Tumor weight is calculated using the equation (length x width^2/2) = mg tumor weight.

Body weight measurement
Mice are weighed twice weekly at the time of tumor measurement.

Compound Preparation
Compounds are prepared in a vehicle consisting of DMSO, Cremophore and PBS.

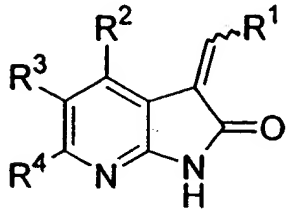
Experimental therapy
Drug therapy begins when the average tumor size is approximately 40-50 mg, which usually is day 7 after implant. The dose schedule consists of one dose/day for 5 consecutive days. Drugs are administered at 3 or 4 dose-levels based upon the previously-determined maximally tolerated dose. A vehicle control group is also included. Drugs may be administered by either i.v., i.p., s.c., or oral (p.o.) transdermal routes or other alternative routes. Drugs may be administered via tail vein infusion. The injection volume administered for each mouse is usually 0.01-0.02 mL/g of body weight. In the case of i.v. injections and tail vein infusion animals are restrained in a Broome restrainer during handling. Animal are fasted overnight prior to p.o. dosing. The duration of each experiment is typically 28 days from tumor implant.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for cancer conditions, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacologic responses observed may

vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

Claims

1. A compound of formula (I)



(I)

wherein:

R^1 is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R^5, $C(O)R^5$, $C(O)OR^5$, and OR^5, where Het and R^5 are as defined below;

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO_2, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl- $SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-,

-S-, -S(O)-, -S(O_2)-, and -N(R^5)-, where said Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-12} aliphatic, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^6)-, where said C_{1-12} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$, where substituted Het and substituted aryl bear substituents that are any of -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^5)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-12} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

2. A compound of formula (I) as claimed in claim 1 wherein:

R^1 is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R^5, $C(O)R^5$, $C(O)OR^5$, and OR^5, where Het and R^5 are as defined below;

R^2 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-6} aliphatic, CN, NO_2, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl-$SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, where said Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-6} aliphatic, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of

-O-, -S-, -S(O)-, -S(O_2)-, and -N(R^6)-, where said C_{1-6} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$, where substituted Het and substituted aryl bear substituents that are any of -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-6} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10

membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

3. A compound of formula (I) as claimed in claim 1 wherein:

R^1 is Het or aryl, with said Het or aryl optionally substituted by one to four substituents selected from the group consisting of C_{1-6} lower alkyl, halogen, $-(CH_2)_{1-6}OH$, $-O(CH_2)_3N(CH_3)_2$, $-NO_2$, $-OR^5$, $-NH(CO)CH_3$, $-C(O)R^5$, aryloxy, $-C_6H_5SO_2NH_2$, or $-C(O)OR^5$, where Het and R^5 are as defined below;

R^2 is H;

R^3 is Het, Het-R^5, aryl, C_{1-12} aliphatic, $-COR^5$, $-CO_2R^5$, or halogen, and where Het and R^5 are as defined below;

R^4 is H;

R^5 is H, C_{1-12} aliphatic, $-SO_2R^6$, or $-N(R^6)_2$, where said C_{1-12} aliphatic is optionally substituted by one to four of halogen, where R^6 is as defined below;

R^6 is H, or NH_2;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

4. A compound of formula (I) as claimed in claim 1 wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, -O-C_6H_5, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or -C_6H_5-SO_2NH_2;

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -$S(O_2)$-, and -$N(R^5)$-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, aryl- $SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-,

-S-, -S(O)-, -S(O_2)-, and -N(R^5)-, where said Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-12} aliphatic, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^6)-, where said C_{1-12} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$, where substituted Het and substituted aryl are any of -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-12} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

5. A compound of formula (I) as claimed in claim 4 wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH,

C_{1-6} alkoxy, -O-C_6H_5, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$;

R^2 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-6} aliphatic, CN, NO_2, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl-$SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, where said Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-6} aliphatic, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^6)-, where said C_{1-6} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$, where substituted Het and substituted aryl are any of -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-6} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran , benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

6. A compound of formula (I) as claimed in claim 4 wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, -O-C_6H_5, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$;

R^2 is H;

R^3 is Het, Het-R^5, aryl, C_{1-12} aliphatic, $-COR^5$, $-CO_2R^5$, or halogen, and where Het and R^5 are as defined below;

R^4 is H;

R^5 is H, C_{1-12} aliphatic, $-SO_2R^6$, or $-N(R^6)_2$, where said C_{1-12} aliphatic is optionally substituted by one to four of halogen, where R^6 is as defined below;

R^6 is H, or NH_2;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

7. A compound of formula (I) as claimed in claim 4 wherein:

R^1 is phenyl, substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of Br, F, -OH, $-CH_2OH$, $-O-CH_3$, $-O-C_6H_5$, $-O-(CH_2)_3NH_2$, $-C(CH_3)_2$, or $-NHCOCH_3$, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$.

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO_2, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl- $SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-,

-S-, -S(O)-, -S(O_2)-, and -N(R^5)-, where said Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, -NO_2, halogen, -OR^5, -SR^5, -S(O)R^5, -NR^5R^7, -NR^5COR^5, -$NR^5CO_2R^5$, -$NR^5CONR^5R^7$, -$NR^5SO_2R^5$, -$NR^5C(NR^5)NHR^5$, -COR^5, -CO_2R^5, -$CONR^5R^7$, -$SO_2NR^5R^7$, -$OCONR^5R^7$, or -$C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5, and where Het, fused Het, R^5 and R^7 are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-12} aliphatic, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^6)-, where said C_{1-12} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$, where substituted Het and substituted aryl are any of -CN, -NO_2, -R^6, -SR^6, -OR^6, -$N(R^6)_2$, -S(O)R^6, -SO_2R^6, -$SO_2N(R^6)_2$, NR^6COR^6, -$NR^6CON(R^6)_2$, -$NR^6(NR^6)NHR^6$, -CO_2R^6, -$CON(R^6)_2$, -$NR^6SO_2R^6$, -$OCON(R^6)_2$, or -$NR^6CO_2R^6$ and where Het and R^6 are as defined below;

R^6 is H, C_{1-12} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyrrole, furan, thiophene, pyrazole, or indole.

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5, where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

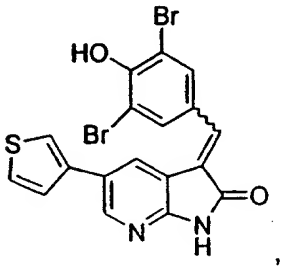
8. A compound as claimed in any one of claims 1 to 7, wherein R^1 is phenyl substituted at the para- position by -OH and said -OH is conjugated with a carbamoyl conjugate to yield a biohydrolyzable carbamate wherein said carbamoyl conjugate is selected from the group consisting of diethylaminocarbonyl, N-(2-hydroxyethyl)aminocarbonyl, N,N,-bis(2-hydroxyethyl)aminocarbonyl, hydroxyethyloxyethylaminocarbonyl, 4-morpholinocarbonyl and 4-methyl-1-piperazinylcarbonyl.

9. A compound as claimed in any one of claims 1 to 7, wherein R^1 is phenyl substituted at the para-position by -OH and said -OH is conjugated with a carbonate conjugate to yield a biohydrolyzable carbonate wherein said carbonyl conjugate is selected from the group consisting of phenylmethyloyxcarbonyl, ethyloxycarbonyl, isobutyloxycarbonyl, and pyridinemethyloxycarbonyl.

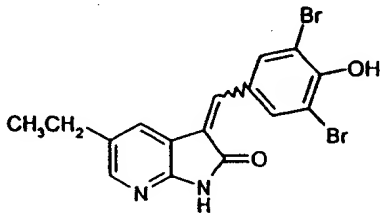
10. A compound as claimed in any one of claims 1 to 7, wherein R^1 is phenyl subsituted at the para-position by -OH and said OH is conjugated with an ester

conjugate to yield a biohydrolyzable ester wherein said ester conjugate is selected from the group consisting of t-butylcarbonyloxymethyl.

11. A compound as claimed in claim 1, selected from the group consisting of

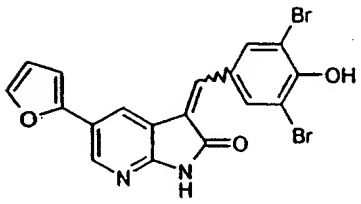


,

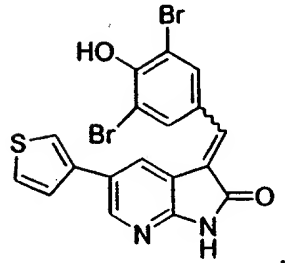


,

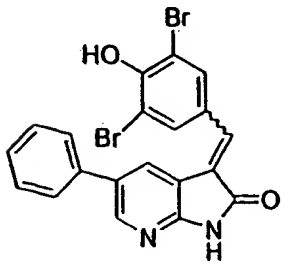
and



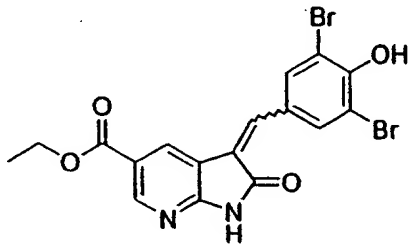
12. A compound as claimed in claim 1, selected from the group consisting of



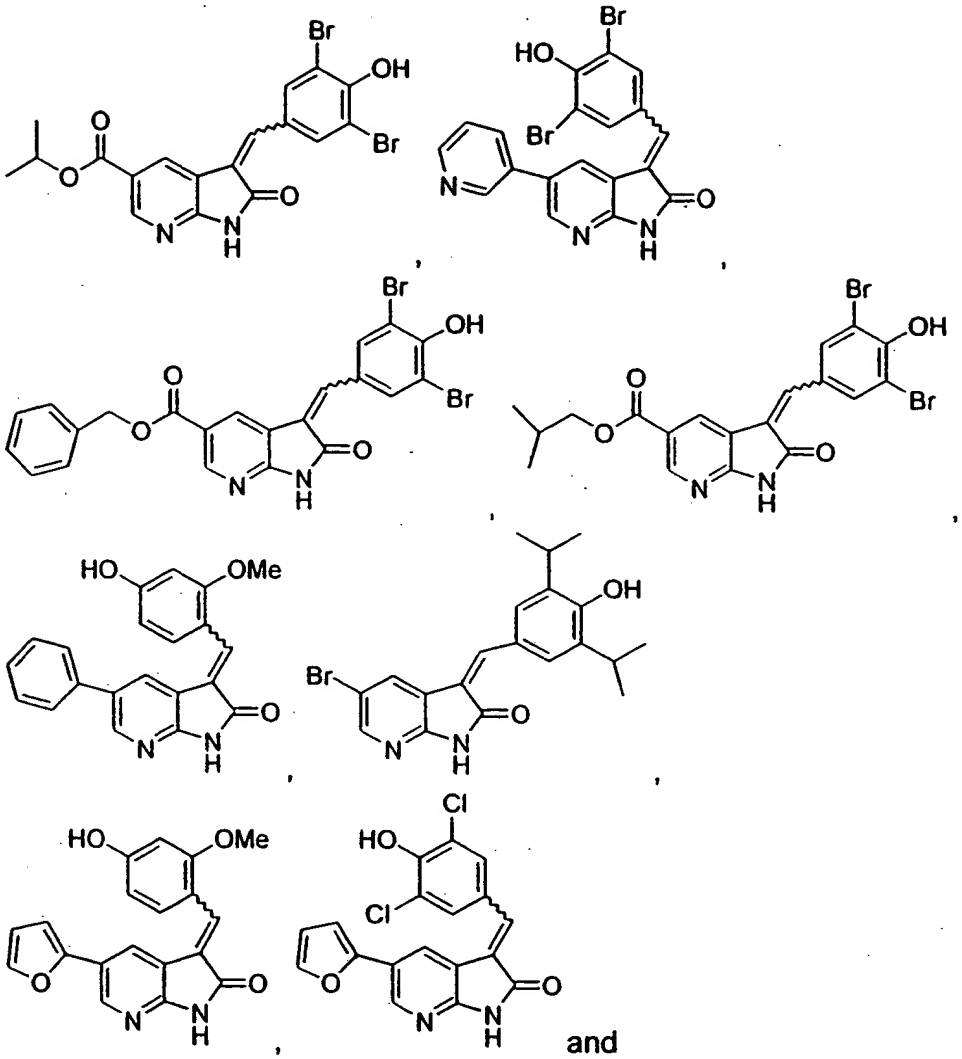
,



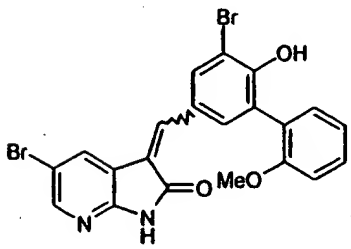
,



,



and



13. The compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

14. The compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

15. The compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-3-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

16. A compound as claimed in any one of claims 1 to 15, wherein said compound is in the E geometric isomer form.

17. A compound as claimed in any one of claims 1 to 15, wherein said compound is in the Z geometric isomer form.

18. A compound as claimed in any one of claims 1 to 15, wherein said compound is a mixture of the Z geometric isomer form and the E geometric isomer form.

19. A compound as claimed in any one of claims 1 to 15, having a chiral carbon atom and which compound is dextrorotatory.

20. A compound as claimed in any one of claims 1 to 15, having a chiral carbon atom and which compound is levorotatory.

21. A compound as claimed in any one of claims 1 to 15, having a chiral carbon atom and which is a mixture of dextrorotatory and levorotatory.

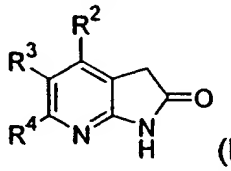
22. A compound as claimed in any one of claims 1 to 21 for use in therapy.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

24. A process for the preparation of a compound of formula (I) as claimed in claim 1, which comprises the reaction of a compound of formula (II)

R^1CHO (II)

wherein R^1 is as defined in claim 1,with a compound of formula (III)



(III)

wherein R^2, R^3 and R^4 are as defined in claim 1.

25. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by a mitogen activated protein kinase.

26. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by a kinase selected from the group consisting of ab1, ATK , bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6 , cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie_1, tie_2, TRK, UL97, Yes and Zap70.

27. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease meditated by cRaf1 kinase.

28. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease meditated by p38 kinase.

29. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease meditated by VEGFR kinase.

30. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease meditated by Tie2 kinase.

31. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease meditated by c-fms kinase.

32. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for inhibiting tumor growth, preventing organ transplant rejection, healing a chronic wound, or for treating a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation, and neurodegenerative disease.

33. A method of treating a disease mediated by a mitogen activated protein kinase, comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

34. A method of treating a disease mediated by a kinase selected from the group consisting of ab1, ATK , bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6 , cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie_1, tie_2, TRK, UL97, Yes and Zap70, said method

comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

35. A method of treating a disease meditated by cRaf1 kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

36. A method of treating a disease meditated by p38 kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

37. A method of treating a disease meditated by VEGFR kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

38. A method of treating a disease meditated by Tie2 kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

39. A method of treating a disease meditated by c-fms kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

40. A method of inhibiting tumor growth, preventing organ transplant rejection, healing a chronic wound, or of treating a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis,

atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation, and neurodegenerative disease, comprising the step of administering to a patient in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 //(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 16964 A (PHARMACIA) 6 June 1996 see claims 1,6	1,23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 1999	17/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

PCT/EP 98/ 06357

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 33 to 40
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 33 to 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9616964 A	06-06-1996	AU 3926295 A	19-06-1996
		CA 2180730 A	06-06-1996
		CN 1139929 A	08-01-1997
		EP 0741726 A	13-11-1996
		FI 962954 A	24-07-1996
		HU 74875 A	28-02-1997
		JP 9508924 T	09-09-1997
		NO 963066 A	23-07-1996
		NZ 295668 A	24-11-1997
		PL 315689 A	25-11-1996
		US 5719135 A	17-02-1998
		ZA 9509927 A	10-06-1996